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COMPARING THE INCIDENCE OF ACUTE RENAL FAILURE IN PATIENTS WITH EPILEPSY EXPOSED TO LEVETIRACETAM VERSUS OTHER ANTIEPILEPTIC DRUGS

Sponsor:

UCB Biopharma SRL

Allée de la Recherche 60

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July 30th 2021

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PASS INFORMATION

Title	Comparing the incidence of acute renal failure in patients with epilepsy exposed to levetiracetam versus other antiepileptic drugs
Version identifier of the final clinical study report	N/AClinical Study report V 2.0
Date of last version of Study Report	30th July 2021
European (EU) Post-Authorization Study (PAS) register number (if applicable)	EUPAS26595
Active substance	Levetiracetam, lamotrigine, phenytoin, valproic acid, carbamazepine, gabapentin, topiramate, oxcarbazepine, pregabalin, phenobarbital, zonisamide, lacosamide, ethosuximide
Medicinal product	Levetiracetam, lamotrigine, phenytoin, valproic acid, carbamazepine, gabapentin, topiramate, oxcarbazepine, pregabalin, phenobarbital, zonisamide, lacosamide, ethosuximide
Product reference	N03AX14
Procedure number	EMEA/H/C/000277/II/0162.
Marketing Authorisation Holder	UCB Biopharma SPRL
Joint PASS	No
Research question and objectives	This study is being conducted to compare the incidence of acute renal failure in patients with epilepsy exposed to levetiracetam versus other antiepileptic drugs in order to further review the association between exposure to levetiracetam and acute renal failure using real world data from a claim database in the US
Country of study	USA
Author	[redacted], [redacted] UCB Pharma

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1 ABSTRACT

Title

Comparing the incidence of acute renal failure in patients with epilepsy exposed to levetiracetam monotherapy or polytherapy versus other antiepileptic drugs

Keywords

Antiepileptics, acute renal failure, adverse reaction, epilepsy

Rationale and background

Following a review of case-reports suggesting a link between the occurrence of acute renal failure (ARF) and levetiracetam (LEV) administration and requests for more information on this topic from several regulatory agencies worldwide, the UCB Benefit Risk Team decided to conduct the present study to further characterize the risk of acute renal failure in patients exposed to LEV and other antiepileptic drugs (AEDs). The study was agreed with the EMA during procedure EMEA/H/C/000277/II/0162.

Research question and objectives

The research question addressed by this project is as follows: Is the incidence rate of acute renal failure higher in patients with epilepsy exposed to LEV treatment compared to patients with epilepsy exposed to other AEDs?

The objective of the study was to compare the incidence rate of ARF among patients newly exposed to LEV versus other AEDs (as "Monotherapy or "Polytherapy") to further characterize the risk of renal failure in patients treated with AEDs.

Variables and data sources

The incidence rates (IR) of ARF in new users of LEV was compared to the IR in new users of carbamazepine (CBZ), ethosuximide (ESX), gabapentin (GBP), lacosamide (LCM), lamotrigine (LTG), oxcarbazepine (OXC), phenobarbital (PHB), phenytoin (PHT), pregabalin (PGB), topiramate (TPM), valproic acid (VPA), and zonisamide (ZNS) alone ("Monotherapy") or when prescribed with other AEDs concomitantly ("Polytherapy"), using High Dimensional propensity score and Inverse Probability of Treatment weight analysis in the IBM® MarketScan® Databases.

Study design

Retrospective cohort study

Setting

The analysis was conducted using the IBM® MarketScan® Databases, a US claims database including both inpatients and outpatients records with a population coverage of almost 200 Million patients.

Subjects and study size, including dropouts

163,569 (78,394 LEV and 85,175 other AEDs) patients with an epilepsy diagnosis and a new prescription of AEDs as "Monotherapy" and 125,541patients (44,668 LEV and 80,873 other AEDs) as "Polytherapy" were identified between 2009 and 2017. After applying inclusion/exclusion criteria and propensity score weighting, 110,336 (45,672 LEV and 64,664

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other AEDs) "Monotherapy" patients and 96,215 (30,426 LEV and 65,789 other AEDs) "Polytherapy" patients were analyzed.

Results

The overall crude rate of ARF following the use of a new AED in the study was **6.0 ARFs per 10,000 patients** and **6.5 per 10,000 patients** for patients using AEDs in "Monotherapy" and in "Polytherapy" respectively in the first 30 days after index date. The IRR of ARFs in LEV new users compared to all other AED new users in "Monotherapy" was 1.37 CI95% (0.8, 2.34) in the first 30 days after index date. Such an increase in risk represented 2 additional LEV ARF cases per 10 000 patients-months in "Monotherapy" compared to all other AEDs. When comparing new users of LEV to new users of other AEDs in "Polytherapy" in the first 30 days of use, the IRR was 0.94 CI95% (0.51, 1.74). IRRs of 1.07 for "Monotherapy" and 1.19 for "Polytherapy" were found when adding secondary ARF codes to the outcome definition.

Discussion

This study presents a new AEDs users design comparing the risk of ARF in LEV to other AEDs users, using an optimal short risk-window and a state-of-the-art analytical pharmacoepidemiology methods (High Dimensional Propensity Score and Inverse Probability of Treatment weights) in order to assess the risk of ARFs in new users of LEV vs other AEDs when used alone or concomitantly with other AEDs. The rate of ARFs in AED new users was found to be very low which decreased the power of 1:1 analyses that compare LEV to other AEDs one by one, leading to remaining covariates imbalance after weighting. Analyses showing a satisfactory balance in covariates, showed a weighted IRR 1.37 CI95% (0.8, 2.34)) in ARF rates of LEV versus other AED users when used as "Monotherapy" (combined comparator AEDs into one comparison group) and a weighted IRR 0.94 CI95% (0.51, 1.74)) when used as "Polytherapy" in the IBM® MarketScan® Research Databases. Such an increase in risk represented 2 additional LEV ARF cases per 10 000 patient months in "Monotherapy". The risk of ARF in LEV users in the study is aligned with the current information included in the EU SmPC. The results of the study do not impact the current benefit-risk balance of the product.

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2 LIST OF ABBREVIATIONS

AED	Antiepileptic drug
AKI	Acute kidney injury
ARF	Acute Renal Failure
CBZ	Carbamazepine
CCAE	IBM MarketScan® Commercial Database
CDHP	Consumer-Driven Health Plan
CI	Confidence Interval
CNS	Central Nervous System
CPT	Current Procedural Technology
EMA	European Medicines Agency
EMR	Electronic Medical Record
EPO	Exclusive Provider Organization Plan
ESX	Ethosuximide
FAERS	FDA Adverse Event Reporting System
FDA	Food and Drug Administration
GBP	Gabapentin
HCUP	Healthcare Cost and Utilization Project
HDHP	High-Deductible Health Plan
HDPS	High-Dimensional Propensity Score
HIPPA	Health Insurance Portability and Accountability Act
HMO	Health Maintenance Organization Plan
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
ICD-10-CM	Internal Classification of Diseases, Tenth Revision, Clinical Modification
IPTW	Inverse Probability of Treatment Weights
IR	Incidence Rate
IRR	Incidence Rate Ratio
LCM	Lacosamide
LEV	Levetiracetam
LTG	Lamotrigine
MDCD	IBM MarketScan® Multi-State Medicaid Database
MDCR	IBM MarketScan® Medicare Supplemental Database

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MHPD	Market Health Product Directorate
NDC	National Drug Code
OTH	All other AEDs
OXC	Oxcarbazepine
PGB	Pregabalin
PHB	Phenobarbital
PHT	Phenytoin
PI	Prescribing Information
POS	Point-of-Service Plan
PPO	Preferred Provider Organization Plan
PRAC	Pharmacovigilance Risk Assessment Committee
PS	Propensity Score
RCT	Randomized Controlled Trial
TPM	Topiramate
US	United States
VPA	Valproate / valproic acid
WHO	World Health Organization
ZNS	Zonisamide

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3 RESPONSIBLE PARTIES

This study was sponsored and conducted by UCB Pharma SA.

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4 OTHER RESPONSIBLE PARTIES

A list of all collaborating institutions and investigators can be obtained upon request.

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5 MILESTONES

Table 6–1: List of study milestones

Milestone	Dates
Date of data extraction	April 1st 2020
Date of final analytical data set	April 30th 2020
Registration in the EU PAS registry	December 10th 2018
Final study report	June 30th 2020
Clinical Study report V0.2 (with amendment 1) [1]	June 30 th 2021

6 RATIONALE AND BACKGROUND

Epilepsy is a condition characterized by at least two unprovoked (or reflex) seizures occurring greater than 24 hours apart or one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years(1). It is one of the most common neurological disorders of the brain, affecting approximately 70 million people worldwide(2). There are approximately 20 AEDs available on the market with diverse mechanisms of action, and efficacy and safety profiles. The choice of AEDs is primarily based on evidence of efficacy for the patient's seizure type, safety profile of the drug and patient-specific factors including age, sex, childbearing potential, comorbidities, and use of concomitant medications(3). Monotherapy is recommended for patients with newly diagnosed epilepsy. Combination therapy is usually initiated upon unresponsiveness to monotherapy. Adverse effects of AEDs are common and can have a considerable impact on quality of life and contribute to treatment failure in up to 40% of patients(4). The adverse effect profiles of AEDs differ greatly and are often a determining factor in drug selection because of the similar efficacy rates shown by most AEDs. UCB identified a published case-report suggesting a link between the occurrence of ARF and LEV administration (5). Following this, the Marketed Health Product Directorate (MHPD) of Health Canada requested UCB to submit a summary of adverse events and serious adverse drug reactions of acute renal injury in patients exposed to LEV. UCB then received another similar request from Medsafe, the New Zealand Medicines and Medical Devices Safety Authority. Both health authority requests appeared to be in response to a signal assessment conducted by the World Health Organization (WHO) on impaired renal function, including ARF and interstitial nephritis in association with LEV exposure(6). UCB thus conducted a comprehensive safety signal assessment and confirmed the risk of ARF after exposure to LEV. A signal assessment specific for interstitial nephritis was also conducted but the risk was not confirmed. Consequently, the term “acute kidney injury” was added to section 4.8 undesirable effects of the CCDS for LEV in the post-marketing experience sub-section and under renal and urinary disorders system organ class. Acute Kidney Injury (AKI) is another term for Acute Renal Failure (ARF). It is often used interchangeably by the medical field. Additionally, following a review of the US Prescribing Information (PI) to add AKI submitted on the 29th of April 2016,

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[1] The current version of the study report has been amended to address statistical errors found in the analysis at the time of manuscript preparation. The corrected analysis does not change the conclusions of the report.

the Food and Drug Administration (FDA) requested UCB on the 25 Oct 2016 to update the labeling to include interstitial nephritis in post-marketing experience section 6.2. The UCB Benefit Risk Team decided to conduct the present study to further characterize the risk of ARF in patients exposed to LEV and other AEDs. Subsequently, UCB received an assessment report (Procedure No. EMEA/H/C/000277/II/0162) from the EMA on 23 Aug 2016 with a request to investigate the actual mechanism underlying the development of ARF after use of LEV. The EMA acknowledged that the proposed study would not provide any information on the underlying mechanism for developing ARF, but agreed to the study. This study is being conducted to further review the association between exposure to LEV and ARF using real world data from a claims database in the US in order to further characterize this risk with respect to other AEDs.

7 RESEARCH QUESTION AND OBJECTIVES

The objective of the study was to compare the incidence rate of ARF among patients newly exposed to LEV versus other AEDs (as monotherapy or polytherapy) to further characterize the risk of renal failure in patients treated with AEDs.

The research question addressed by this project is as follows: Is the incidence rate of ARF higher in patients with epilepsy exposed to LEV treatment compared to patients with epilepsy exposed to other AEDs?

The following hypothesis will be addressed:

- Null hypothesis (H0): The incidence rate of ARF in patients with epilepsy exposed to LEV (as monotherapy or polytherapy i.e. LEV in combination with other AEDs) is the same as in patients with epilepsy exposed to other AED monotherapy regimens or AED polytherapy regimens excluding LEV.

- Alternative hypothesis (H1): The incidence rate of ARF in patients with epilepsy exposed to LEV (as monotherapy or polytherapy i.e. LEV in combination with other AEDs) is different from patients with epilepsy exposed to other AED monotherapy regimens or AED polytherapy regimens excluding LEV.

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8 STUDY PROTOCOL AMENDMENTS AND UPDATES

Table 8–1: Protocol amendments

Number	Date	Section of study protocol	Amendment or update	Reason
V0.2	12-Apr-2017	N/A	Update	Initial submission to EMA
V0.3	18-Sep-2017	N/A	Update	1st Response to Questions from EMA
V0.4	12-Feb-2018	N/A	Update	2nd Response to Questions from EMA. Protocol approved by EMA with fulfilment of post-approval measure EMEA/H/C/000277/MEA/086.3 on 31st May 2018
V1.0	15-Apr-2020	N/A	Update and Amendments	Protocol amended. Last version of the protocol uploaded in EU PAS Register at http://www.encepp.eu/encepp/viewResource.htm?id=35130 and submitted to EMA on 15th April 2020

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9 RESEARCH METHODS

9.1 Study design

Retrospective cohort study conducted using the US-based claims database, IBM® MarketScan® Research Databases.

9.2 Setting

The IBM® MarketScan® Research Databases covers the period between 01-Jan-2008 and 31-Dec-2017.

9.3 Study participants

US population of patients with an epilepsy diagnosis, with a new prescription of LEV or comparator AEDs, as monotherapy or polytherapy. The following 12 AED monotherapy comparator cohorts were evaluated in the study: carbamazepine (CBZ), ethosuximide (ESX), gabapentin (GBP), lacosamide (LCM), lamotrigine (LTG), oxcarbazepine (OXC), phenobarbital (PHB), phenytoin (PHT), pregabalin (PGB), topiramate (TPM), valproic acid (VPA), and zonisamide (ZNS). The "Monotherapy" analysis includes patients who are AED naïve for at least one year (baseline) and start a new treatment of LEV or of one of the 12 AEDs listed above. For

"Polytherapy", two cohorts were evaluated; patients on a LEV-based polytherapy regimen were compared with a cohort of patients on all other AED polytherapy regimens that do not include LEV as explained in the "polytherapy" definition below. These patients were treated with any AEDs (one or several, except LEV) during the year preceding the index date when a new treatment of AED (different from those given during baseline) is introduced. Details of the study population are indicated below.

9.4 Variables

9.4.1 Inclusion criteria

Patients were eligible for inclusion in the study if they met all of the following criteria:

1. A diagnosis of epilepsy (as defined below) during the baseline period
2. Initiation of treatment with either LEV or comparator AED (as monotherapy or polytherapy as defined in sections 9.4.3.1 and 9.4.3.2, respectively) within the patient selection period without prior treatment for the specific AED in the 12 months prior.
   a) If the patient's index AED prescription occurs after 12 months (baseline) without any AED use, the patient will be included in the monotherapy cohort
   b) If the patient's index AED prescription occurs after having already used AEDs during the 12 preceding months (baseline) the patient will be included in the polytherapy/switching cohort.
3. Continuous medical and prescription benefit coverage during the baseline period

Patients were classified as having an epilepsy diagnosis if they fulfill any of the criteria indicated below:

- The presence of ≥ 2 ICD-9-CM codes of 780.39 (seizure symptoms) during separate medical encounters, specifically different dates of care in any medical care venue that are separated by at least 1 day
- An occurrence of ≥1 ICD-9-CM code of 780.39 AND ≥1 ICD-9-CM code of 345.xx (excluding 345.3) during separate medical encounters, specifically different dates of care in any medical care venue that are at least 1 day apart, when the first code identified during the baseline period is 780.39
- An occurrence of at least one ICD-9-CM code of 345.xx (excluding 345.3)
- Patients with ICD-9-CM code of 345.3 will be required to have
  - an occurrence of ≥2 ICD-9-CM codes of 345.3 separated by at least 30 days
  - or an occurrence of the ICD-9-CM code 780.39 followed by 345.3 code and separated by at least 30 days,
  - or ≥1 ICD-9-CM code 345.3 and ≥1 ICD-9-CM code 345.xx encounters on separated by at least 30 days

The ICD-9-CM and ICD-10-CM codes for epilepsy were identified in the baseline period and are listed in protocol appendix 2. The validity of the algorithms that are being used to identify

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patients with epilepsy have been investigated in multiple studies. The performance of the algorithms was very variable. The positive predictive values varied widely across populations between 21% and 98%, the sensitivity ranged between 86% and 99%, whilst the specificity varied between 85% and 93% (7, 8).

9.4.2 Exclusion criteria

Patients were excluded from the study if they met any of the following criteria:

Monotherapy analyses:

4. Patients with a prescription of any AED during baseline period were excluded
5. Patients starting 2 or more AEDs on index day were excluded

Polytherapy analyses:

6. Patients with a prescription of LEV or index AED during baseline were excluded
7. Patients without any prescription of AED during baseline were excluded

The rest of the criteria are applicable to both monotherapy and polytherapy:

8. We excluded patients with preexisting renal disease to identify new cases of ARF after exposure to the index AED. Therefore, patients with a diagnosis claims of renal dysfunction and renal failure (ICD-9-CM 580.xx to 588.xx; 590.xx;) or use of dialysis (ICD-9-CM codes of, V45.1, V56.0, V56.1; or the procedure codes 3995), CPT codes for dialysis services of 90935, 90937,90939, 90940, 90945, 90947, 90997, 90999, 99512, 99559 and HCPCS codes G0257; S9335; S9339 in any field of diagnosis / procedure during the baseline period will be excluded.
9. We excluded patients with medical conditions or procedures that cause ARF, when these events occur close to the index date. This will ensure that the outcomes that the cases ARF identified during the follow-up period are attributable to the index AED, not other causal factors proximal to the index date. Therefore, the following patients were excluded:

- Patients with a claims record of diagnosis of rhabdomyolysis (ICD-9-CM 728.88) in the 90 days prior to the index date.
- Patients with a claims record of a diagnosis of status epilepticus (ICD-9-CM 345.3) within 90 days prior to the index date
- Patients with a record of a hospitalization and a claims record indicating the patient had a major surgical procedure within 30 days prior to the index date
- Procedures using radiocontrast agents within 30 days prior to the index date

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9.4.3 Exposure: Treatment assessment

Patients were considered as having continuous treatment coverage if the gaps between the supply of their consecutive prescriptions are less than 30 days. Patients were considered exposed to AED treatments 30 days after the date of last prescription + days of supply. Benzodiazepines except for clonazepam and clobazam were excluded from analyses assessing type of AED treatment. The mode day's supply of the non-missing, non-null, non-negative values were obtained for each AED prescribed (see protocol Appendix 1) for each patient. This was used for imputation of prescription records with null, negative, or missing values of the days' supply during the study period. In case only one claim is present, or no mode exists, the mode of the non-missing, non-null, non-negative values for that AED for all patients were used. Prescriptions with more than 90 days of drug supply were truncated at 90 days.

9.4.3.1 Monotherapy

Patients were classified as having received AED monotherapy treatment if their first registered pharmacy claims records for the index AED were preceded by a 12 months minimum continuous enrolment in the database without any AED claims. Patients receiving two or more AEDs on the same date were excluded from the analysis.

Exposure to AED started from index date (first AED prescription registered in the database preceded by a minimum 12 months continuous enrolment period) and ended at the earliest of (Figure 9-1):

- Discontinuance of insurance coverage
- End of risk time-window (30 (main analysis), 60 or 90 (sensitivity analysis) days post index date)
- End of the study period
- First diagnosis of acute renal failure

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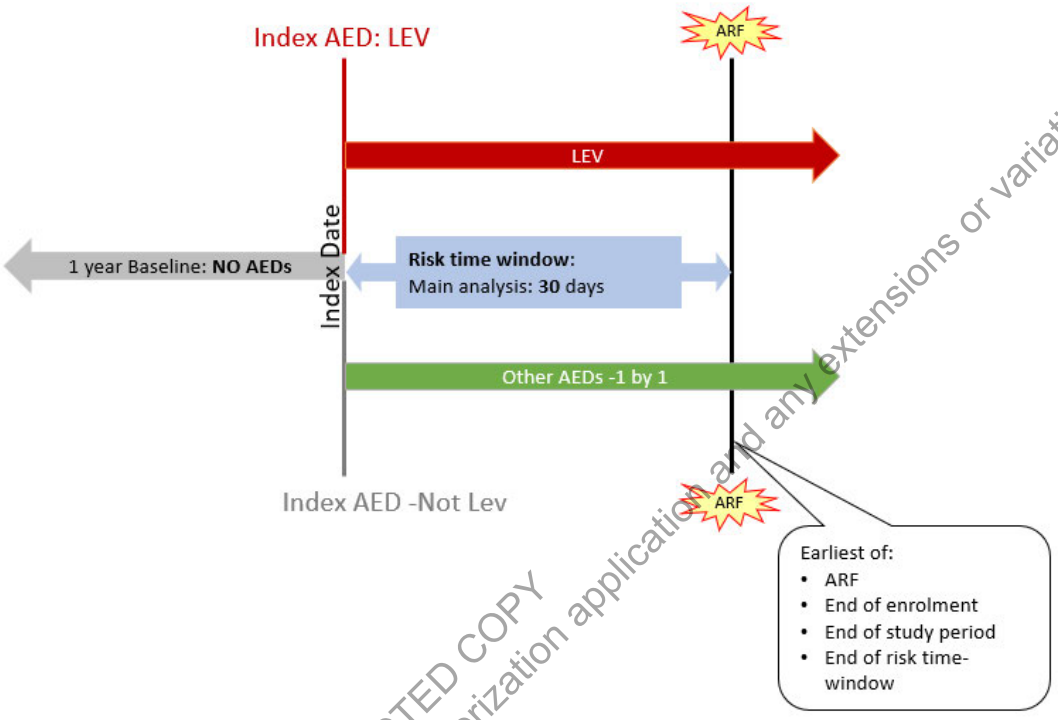
Figure 9-1 Monotherapy design (Patients starting > 1 AED on index date are excluded)



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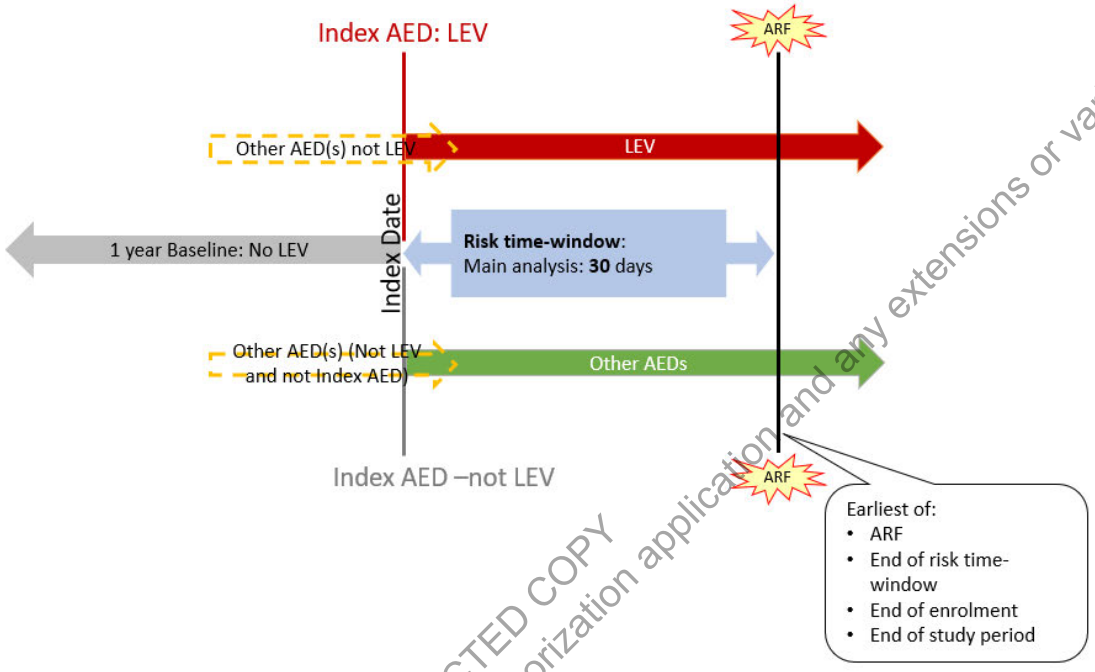
9.4.3.2 Polytherapy: Switchers or patients adding-on a new AED

The "Polytherapy" analysis included patients adding a new AED to their regimen or switching to the index AED of interest. During the first weeks after the start of a new AED in patients having received previous AED prescriptions, patients are often taking more than one drug as they experience a period of so called "cross titration" where they are still on the former AED but start taking the new one. During this "cross titration" period which is also the period of highest risk for ARF (30 days), it is not possible to ascertain when patients are taking the drug in monotherapy or concomitantly with other AEDs (polytherapy). Therefore, this analysis considered all the epilepsy patients already exposed to AED treatment at baseline and receiving a new treatment of AED (different from those given during baseline) as potentially under polytherapy during the risk time window of the study. Exposure to AEDs started from the index date (first new treatment of AED after a minimum period of 12 months continuous enrolment) and ended at the earliest of (Figure 9-2):

- Discontinuance of insurance coverage
- End of risk time-window (30 (main analysis), 60 or 90 (sensitivity analysis) days after index date)
- End of the study period
- First diagnosis of acute renal failure

Figure 9-2 Polytherapy design: Switch and add-on patients continuing AED treatment



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9.4.4 Outcome

Patients were classified as having ARF if they had a diagnosis claim of at least 1 inpatient or 1 emergency department with the ICD-9-CM diagnoses codes of 584.0 (acute renal failure, unspecified), 584.5 (acute tubular necrosis), 584.6 (cortical acute renal failure), 584.7 (medullary acute renal failure), 584.8 (acute renal failure with other specified pathologic lesion) and 584.9 (acute renal failure, not otherwise specified) or ICD-10-CM diagnoses codes of N17.0 (acute kidney failure with tubular necrosis), N17.1 (acute kidney failure with acute cortical necrosis), N17.2 (acute kidney failure with medullary necrosis), N17.8 (other acute kidney failure), or N17.9 (acute kidney failure, unspecified), as the principal diagnosis (using guidance for previous studies and the FDA sentinel case definition of ARF), during the follow-up period(9, 10)

9.4.5 Other variables

9.4.5.1 Characteristics of patients

The following patient characteristics were described at index date: age, gender, region of residence, and type of database. Patients were stratified by age in years in these categories: 1-<4, 4-17, 18-45, 46-64, 65+years. The region of residence was classified as Northeast, North Central, South or West regions of the US. Database type will be classified as Commercial/Medicare and Medicaid.

9.4.5.2 Baseline comorbidities

The prevalence of comorbidities associated with the risk of renal failure(11) in the baseline period were estimated including burns, cardiovascular disease, cerebrovascular disease, chronic obstructive pulmonary disease, diabetes mellitus, diabetic nephropathy, heart failure, hemolysis, hypertension, hypotension, hypovolemia, liver disease, myoglobinuria, obesity, other renal diseases, peripheral vascular disease, proteinuria, renal calculi, sepsis, small kidney of unknown cause, and systemic lupus erythematosus. A patient was identified as having comorbidity if they had at least 1 inpatient or 2 outpatient claims (encounters on separate days) with the ICD-9-CM code of interest (protocol appendix 3), as a principal diagnosis, during the baseline period. Furthermore, the burden of chronic medical conditions in the baseline period was estimated using the Healthcare Cost and Utilization Project (HCUP) Chronic Condition Indicator which categorizes ICD-9-CM diagnosis codes as chronic or not chronic (HCUP, 2011). Chronic conditions are defined as lasting ≥12 months and either (a) place limitations on self-care, independent living, and social interactions or (b) result in the need for on-going intervention with medical products, services, and special equipment.

These baseline comorbidities were used to assess the balance in the baseline characteristics between the comparator groups after implementing the high-dimensional propensity score (HDPS) model.

9.4.5.3 Baseline medications

The total number of prescriptions during the baseline was estimated at the generic drug level, and the proportion of patients who had at least one prescription claim of any of the medications in the drug classes listed in appendix 4 of the protocol. The total number of previous AEDs prior to the index date was also estimated. These characteristics were used to assess the balance in the baseline characteristics between the comparator groups after implementing the HDPS model.

9.4.5.4 Baseline health care utilization

The overall number of health visits (inpatients, outpatients, emergency department visits) in the baseline period was also estimated. These characteristics were used to assess the balance in the baseline characteristics between the comparator groups after implementing the HDPS model.

9.5 Data sources and measurement

The analysis was performed using the IBM® MarketScan® Commercial Database (CCAE 2017 v1 0), the IBM® MarketScan® Medicare Supplemental Database (MDCR 2017 v1.0), and the IBM® MarketScan® Multi-State Medicaid Database (MDCD 2017 v1.0). This is an US based database. The database contains information of over 125 million covered lives comprising of commercially insured individuals (i.e. working age adults and their dependants), patients aged 65 years and older with Medicare coverage plus employer-paid commercial plans and individuals with limited resources whose insurance is paid by the state respectively. The database captures information on medical (inpatient, outpatient, and emergency care) and pharmacy claims information, as well as enrolment history. The medical service claims record detailed information

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for inpatient and outpatient healthcare encounters, including date and place of service, provider type, plan- and patient-paid amounts, International Classification of Diseases, 9th and 10th Revisions, Clinical Modification (ICD-9-CM and ICD-10-CM) diagnosis and procedure codes, and CPT-4 procedure codes. Pharmacy claims include information on dispensed medications including National Drug Code (NDC), dispense date, quantity, days supplied, and plan- and patient-paid amounts. The enrolment file contains information on age, gender, US census region, health insurance payer type, and monthly enrolment status. These files are linkable based on an encrypted patient identification number.

9.6 Bias

Below a list of potential study strength and limitation anticipated at the design stage:

- The study population is limited to patients with Commercial, Medicare Supplemental or Medicaid insurance coverage, and therefore results may not be representative of the entire US population, as uninsured patients are not included in the database. Risk factors for dose-dependent drug induced ARF have been well described in literature. However, there is very limited data published on idiosyncratic drug induced ARF; most of the available data is available from case reports(12). Although there may be differences in the socioeconomic characteristics in the patients included in the database and patients that are excluded due to lack of insurance, it is assumed that the underlying risk factors of idiosyncratic ARF are non-differential and therefore would not have a significant impact on the study estimates.
- There might be missing information, miscoding or underreporting of disorders in the claims data. Ascertainment of drug exposures, diagnoses, and procedures depends on the precision available in coding systems and the accuracy with which codes are assigned to services. The exposure and outcome variables will be identified using validated algorithms which have been identified to have high specificity. Valid relative effect measures can still be estimated when the specificity of a test is high under the assumption of non-differential misclassification across treatment groups (13, 14). Additionally, sensitivity analyseswill be conducted to assess the impact of the algorithms on the effect estimates.
- Insurance claims are financial records in which the diagnosis is the justification for the medical service. Tentative, rule-out diagnoses can be difficult to distinguish from confirmed diagnoses. When defining the outcomes in the primary analysis, we have limited them to the principal diagnoses has been known to represent the main diagnosis. A sensitivity analysis will also be done to assess the impact of using the main diagnosis only versus all diagnoses.
- Patient receipt of a dispensing of an AED is documented in claims data, but there is no record of actual use of drugs. Consequently, there will be some patients who will be misclassified as having been exposed to the index drug even though they did not take the index drug. It is assumed that this will be non-differential across the treatment groups and therefore will have minimal impact on the study results.

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- Information on potential confounders such as lifestyle, occupational, and environmental factors are missing or at best incomplete in claims data. However, most of the well-known risk factors for ARF are comorbidities or medications that are well captured in the database. As such it is anticipated that most of the confounders will be adjusted for in the analyses.
- Finally, the study is not powered to detect moderate changes in the risk of ARF.

However, despite these limitations, there are several advantages of using this database. Because of the large sample size, adequate number of patients will be included in the study to assess the risk of renal failure. Additionally, the data represent real-life management of patients with epilepsy.

9.7 Study size

All patients addressing the inclusion/exclusion criteria were included in the analysis. Below, the former feasibility assessment included previously in the most recent version of the protocol V1.0 is presented. Additional discussion on the power obtained after conducting the analysis can be found in section 11.2.1.

A previous feasibility assessment was conducted in the IBM® MarketScan® Research Databases using the Safety Works software to estimate the number of patients exposed to LEV or other AEDs as monotherapy. Patients were defined as having monotherapy if they had a prescription of an index AED without the prescription of any other AEDs during the follow-up period. Patients were required to have at least one ICD-9-CM code for epilepsy (345) or at least two ICD-9-CM codes for seizures (780.39) in the baseline period of 6 months prior to the index date. The number of patients who had monotherapy are provided in Table 9–1.

Table 9–1: Number of epilepsy patients with AED monotherapy

Description	Total number of patients	Total Outcomes (renal failure)
Levetiracetam	101,424	3,120
Lamotrigine	45,565	501
Phenytoin	38,785	1,152
Valproic acid	33,202	648
Carbamazepine	29,883	406
Gabapentin	29,158	1,218
Topiramate	26,052	296
Oxcarbazepine	20,848	187
Phenobarbital	9,456	204
Pregabalin	7,067	290

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Description	Total number of patients	Total Outcomes (renal failure)
Zonisamide	6,397	70
Lacosamide	3,452	63
Ethosuximide	3,334	4
Clobazam	435	2
Felbamate	260	1
Vigabatrin	149	1
Rufinamide	142	2
Tiagabine	101	3
Eslicarbazepine	96	-
Perampanel	27	1
Retigabine	10	

Based on the number of patients in each AED cohort from the feasibility assessment (Table 9–1), including cohorts with a minimum sample size of 3000, an overall 2-sided 95% confidence interval (and accounting for the multiple comparisons using the Bonferroni test to a confidence interval of 99.995%), a power of 80%, and also assuming the incidence of ARF is 0.5% based on results from a population-based study conducted in the US that estimated the incidence of ARF (15), the minimum difference in the incidence rate ratio of ARF that can be detected ranges from 1.5 to 4.0. There are no published data available estimating the incidence rate of ARF in epilepsy patients in general or in subpopulations of patients exposed to AEDs. These estimates for the baseline incidence rates of ARF were obtained from a community-based study and assumed to be the same across all comparator cohorts(15). The Bonferroni adjustment has been included in the sample size calculation to reduce the chances of obtaining false-positive results (type I errors) as there will be multiple comparisons in this study. Table 9–2 provides further information on the sample size calculations.

Table 9–2: Sample size calculations for the study

Reference proportion	Proportion ratio	Power	Alpha	Sample Size
0.005	4.0	0.800	0.05	1,016
0.005	2.0	0.800	0.05	5,148
0.005	1.5	0.800	0.05	16,608
0.005	4.0	0.800	0.01	1,450
0.005	2.0	0.800	0.01	7,469
0.005	1.5	0.800	0.01	24,326
0.005	4.0	0.800	0.005	2,840

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Reference proportion	Proportion ratio	Power	Alpha	Sample Size
0.005	2.0	0.800	0.005	14,928
0.005	1.5	0.800	0.005	49,137

For this study the attained power for the minimum sample size required (3000 patients) assuming an ARF incidence of 0.005, a level of significance of 0.05 and varying proportion ratios of 4.0, 2.0 and 1.5 was 99.95, 61.21 and 23.23 for a sample size of 3000. Additional power calculations are reported in Table 9–3: Attained power for minimum sample size of 3000. Open Source Epidemiologic Statistics for Public Health (OpenEpi) was used to compute the sample size and power calculations for this study.

Table 9–3: Attained power for minimum sample size of 3000

Reference proportion	Proportion ratio	Power[1]	Power[2]	Alpha	Sample Size
0.005	4.0	99.95	99.92	0.05	3,000
0.005	2.0	61.21	55.16	0.05	3,000
0.005	1.5	23.23	18.19	0.05	3,000
0.005	4.0	99.61	99.45	0.01	3,000
0.005	2.0	37.01	31.33	0.01	3,000
0.005	1.5	8.77	6.09	0.01	3,000
0.005	4.0	97.4	96.6	0.005	3,000
0.005	2.0	14.75	11.42	0.005	3,000

[1]Normal approximation

[2]Normal approximation with continuity correction

9.8 Data transformation

The IBM® MarketScan® Research Databases electronic database comprises of fully adjudicated and paid claims records of integrated longitudinal enrollment, inpatient, outpatient and drug data from multiple payors that has been standardized and de-identified prior to use for the analysis. The source data were transferred from MarketScan® Databases via a Secure File Transfer Protocol (FTP) to a UCB internal server with access protection (landing zone). The data were transferred on a quarterly basis to UCB with full year updates at the end of the year. From the landing zone, the data were moved to a destination folder which had been established specifically for storing the IBM® MarketScan® Databases source data on the processing system, where the data were converted into the native format and indexed via SAS software. This process was conducted only by individuals within UCB who had appropriate access rights to the protected storage area of the

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processing system. Subsequent analysis of the converted data and data extracts were performed using SAS 9.4 software (SAS Institute, Inc., Cary, North Carolina) on the processing system, while creating and storing extracts and results on the same system in separated folders per study.

9.9 Statistical methods

9.9.1 Main summary measures

Means and standard deviations, medians and interquartile range, minimum and maximum values, were used to describe continuous variables, whereas frequencies and percentages were used to describe categorical variables.

9.9.2 Main statistical methods

The incidence rate (IR) was calculated as the total number of new cases diagnosed with acute renal failure during the follow-up period divided by the sum of person-months at risk during follow-up. The person time for each patient was calculated as the total number of days of follow-up from the index date to the censoring date as indicated in section 9.4.3. The incidence rate ratio (IRR) was obtained by dividing incidence rate in the LEV cohort by the incidence rate for each of the comparator cohorts.

The modified Poisson regression model with robust variance estimator was used to estimate the IRs and IRRs of acute renal failure(16). The crude IR and 95% confidence intervals (CI) were calculated as the number of new cases per 10,000 person-months of follow-up and reported separately for each AED treatment cohort. Crude incidence rate ratios and 95% CI based on unweighted samples were computed to compare the incidence rates of ARF between LEV and each comparator AED cohort. Thereafter, to control for confounding, modified Poisson regression model with robust variance estimator was constructed based on truncated stabilized IPTW weighted samples. Adjustment for baseline differences between the LEV and comparator AED cohorts to minimize bias due to confounding was performed using a HDPS which were generated using a multivariate logistic regression model, in order to balance the cohorts with respect to observed patient characteristics in the baseline period. Key variables such as age, sex, region, year of index date, health plan type, database type, along with baseline covariates such as comorbidities, chronic conditions, co-medications, and healthcare utilizations are included into the model as predefined covariates. Besides these predefined covariates, HDPS algorithm selected empirical covariates from 5 data dimensions (inpatient diagnoses, outpatient diagnoses, inpatient procedures, outpatient procedures, outpatient pharmacy dispensing). As the IBM® MarketScan® Research Databases contains multiple coding dictionaries for diagnoses (ICD-9-CM, ICD-10-CM) and for procedures (ICD-9-CM, ICD-10-PCS, CPT, HCPCS), the Clinical Classification Software (CCS) from the HCUP (a Federal-State-Industry partnership sponsored by the Agency for Healthcare Research and Quality) was used to group codes into same set of clinically meaningful categories from different coding systems. Using CCS categories has been shown to improve HDPS confounding adjustment and reduce substantial residual confounding when compared with the RCT findings(17). For outpatient pharmacy dispensing, generic drug name from IBM® RED BOOK® was used. The default number (200) of the most prevalent empirical covariates from each

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dimension were considered in the next prioritization step. The default ranking method "Bross bias formula" was used to prioritize the selected empirical covariates from all 5 dimensions. The top 500 (default) empirical covariates were included in the resulting logistic model. A propensity score is estimated for each subject as a predicted probability of exposure conditional on all covariates using multivariate logistic regression(18).

Once the HDPSs were estimated, they were converted into stabilized IPTW and extreme values were truncated at 1 and 99 percentiles. These truncated stabilized IPTW were applied to create a pseudo-population where the measured covariates are not associated with the outcome, and both the exposed and unexposed groups are standardized to the overall population(19). Graphical displays (e.g. boxplots) and descriptive statistics were used to assess the distribution of the stabilized weights. Generally, a mean of 1 for the weights is viewed as a necessary condition for correct model specification (20, 21). The characteristics of the individuals with outlier weights were examined and if necessary, the model was re-specified and the weights re-estimated, or if the outlier weights were not significant the weights were truncated. After the HDPS have been generated, violations of underlying assumptions were assessed. Positivity violations were assessed by plotting the propensity score distributions in an overlay plot for the comparator groups. To evaluate adequate overlap of the propensity scores, the density distribution of the propensity scores was visually inspected (22). The performance of the model was evaluated by assessing the covariate balance across the treatment groups. Standardized differences were used to compare the mean or prevalence of baseline covariates between the comparator treatment groups in the samples weighted by truncated stabilized IPTW. If covariate imbalances remained, the model was refined by either using interaction terms, or modifying the continuous variables (e.g. splines, polynomials or cubic terms). A separate HDPS model was developed for each comparison of LEV and another AED.

After the final HDPS had been generated, the truncated stabilized weights were applied in the outcome model to generate final adjusted estimates of the overall effect of each exposure of interest. Advantages of IPTW include retention of all study patients and estimate of an average exposure effect in the whole population of eligible patients.

9.9.3 Missing data

Based on summary data provided by IBM MarketScan Databases, there were no missing data for age, gender and enrollment information. For the remaining demographic variables which include region, and health plan type the value "Unknown" was used for missing records. For variables derived using diagnoses, procedures, and prescriptions codes, patients were assumed to have experienced an event or filled a medication prescription if the relevant code(s) were found among their claim records. Otherwise, it was assumed that the patient did not experience the event or were not prescribed the medication. For prescription data, in patients who have initial treatment, missing data were imputed as follows: The mode day's supply of the non-missing, non-null, non-negative values were obtained for each AED prescribed (see protocol appendix 1) for each patient. This was used for imputation of prescription records with null, negative, or missing values of the days' supply during the study period. In case only one claim was present, or no mode existed, the mode of the non-missing, non-null, non-negative values for that AED for all patients was used. Prescriptions with more than 90 days of drug supply were truncated at 90 days.

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9.9.4 Sensitivity analysis

Several sensitivity analyses were conducted. First, sensitivity analyses were conducted to assess the impact of the parameters used in the case definitions of the treatment exposure and study outcome by using the case definitions indicated below:

- Renal failure definition as defined in section 9.4.4 but including claims identified in any field of diagnosis.
- Renal failure case definition including the presence of the ICD-9-CM or ICD-10-CM codes of ARF as defined in section 9.4.4 plus the presence of at least 1 code of renal dialysis, ICD-9-CM codes of, V45.1, V56.0, V56.1; or the procedure codes 3995 , CPT codes for dialysis services of 90935, 90937,90939, 90940, 90945, 90947, 90997, 90999, 99512, 99559 and HCPCS codes G0257; S9335; S9339 in any field of diagnosis / procedure.
- 60 days risk time windows.
- 90 days risk time windows.
- Additional exclusion criterion of a minimum of 30 days continuous enrolment in the database after index date. While this analysis ensures that patients are all enrolled for 30 days and that any episode of ARF would be caught it will, however, also exclude any patient who died or was disenrolled from the database before 30 days because of ARF (or any other reason).
- Monotherapy analysis stopping follow-up at the introduction of a new AED instead of 30 days risk time window if the introduction occurred between index date and end of risk time window.
- Analysis using only ICD-9-CM coding, with data selection until October 2015.

9.9.5 Amendments to the statistical analysis plan

Additional analyses were added post hoc to address the issue of model misspecification for the one-to-one (hereafter referred to as "1:1") "monotherapy" analyses mentioned in section 9.4.3.1.:

- Levetiracetam vs. all other AEDs in one comparison group in order to increase study size (hereafter referred to as "Mono-overall")

In order to verify that the HDPS was performing optimally, we carried out a more classic propensity score including all potential confounders listed in appendix 3 and 4 of the protocol (clinical conditions and medications that could impact the risk of AEDs on ARF).

- Simple propensity score with age as a continuous variable
- Simple propensity score with age as a categorical variable

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9.10 Quality control

The IBM® MarketScan® Research Databases contain information on claims that have been paid and adjudicated. The data are tested for completeness at the client-plan level. In addition, the data are checked for accuracy and completeness by testing selected fields of medical and drug coverage indicators for validity and non-standard values, and quantifying missing fields and records. Only MarketScan Annual Files are used in this study which guarantees the highest completeness level and longitudinal integrity. All codes used for each of the study variables are available in the statistical analysis plan. After finalizing the protocol, a statistical analysis plan was developed as a guide for conducting analysis. The statistical analysis plan was reviewed and approved by the study team before any analysis was conducted. Double programing was used in order to validate the analysis.

In October 2015, IBM® MarketScan® Research Databases transitioned from the use of ICD-9-CM to the use of ICD-10-CM. In order to verify the coherence of ICD-9-CM to ICD-10-CM translations, plots of incidence and prevalence of these codes before and after ICD transition in IBM® MarketScan® Research Databases were carried out as described in Panozzo, 2018 for every variable used in the model(23). For this reason, some ICD-9-CM codelists might have been subject to small changes in order to ensure the continuity of variable definitions with ICD-10-CM. All ICD-9-CM and corresponding translations with ICD-10-CM are available in the statistical analysis plan.

Correction of two programming errors lead to the current amendment of the first study report.

When working on the journal manuscript submission, two errors in statistical programming were discovered.

1. In the analysis, some baseline comorbidities of interest were defined using Clinical Classification Software (CCS) categories from the HCUP (a Federal-State-Industry partnership sponsored by the Agency for Healthcare Research and Quality (see part 9.5.4.2 Baseline comorbidities in study report)). During the analysis, some of these categories were omitted in the computation of the comorbidities (see Table **4** below). This 'missing CCS codes' issue was due to some un-displayable non-breaking 'A0'x or null character '00'x read from the excel file that contained the final chosen CCS categories. These un-displayable characters prevent correct linkage to map the appropriate CCS codes and hence some corresponding ICD codes were missed for the identification of these 4 baseline comorbidities. Tables 7. and 11. in the study report show corrected comorbidities for the monotherapy and polytherapy analyses.
2. We also identified a problem with the java script in the HDPS program (High Dimensional Propensity Score) described in detail below. This caused some dimensions of the propensity score to be omitted during the analysis, therefore affecting the weighted estimates.

Table 4 CCS categories omitted in the baseline comorbidities definitions

Comorbidity of interest	Missing CCS
Cardiovascular Disease	100

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Cerebrovascular Disease	78, 109, 110, 112, 113
Diabetes Mellitus	49
Hypertension	58

The calculation of the High Dimensional propensity score was done through the Pharmacoepidemiology Toolbox (https://www.drugepi.org/dope/software#Pharmacoepidemiology) provided by the Division of Pharmacoepidemiology and Pharmacoeconomics at Brigham and Women's Hospital & Harvard Medical School.
This toolbox provides a number of functionalities as written in its documentation[2] including propensity score matching. For the purpose of this study, only 2 of the provided functionalities were used, i.e. high dimensional variable selection and high dimensional propensity scores.
In EUPAS26595, SAS programs were written to submit necessary parameters and the following 5 data dimensions to the toolbox. Subsequently, the toolbox invoked Java to empirically identify, prioritize, and select proxy covariates for adjustment in logistic regression model to generate propensity scores.

(1) Outpatient drug dispensed
(2) Inpatient diagnoses
(3) Outpatient diagnoses
(4) Inpatient procedures
(5) Outpatient procedures

Unexpected messages were found when log files were reviewed. These messages were generated when the toolbox invoked its Java component for the variable selection step. However, these messages were not warnings or error messages, and the toolbox continued to execute the rest of the steps without aborting the algorithm. A closer look into the log files revealed that, whenever these Java messages appeared, only 1 or 2 data dimensions out of the 5 input data dimensions were being selected for the Proc Logistic regression which produced the required propensity scores. The occurrence of these messages seems to surface in a random manner, that is, it is not related to the number of patients nor the number of outcomes the submitted cohort contained. The SAS macro from the toolbox was modified to detect the message and re-try the Java step until no message was produced.

After addressing the issues, the weighted primary analysis showing the Risk Ratio for ARF for LEV use vs. other antiepileptic drugs was reduced from 1.59 CI95% (0.95, 2.68) to 1.37 CI95% (0.8, 2.34) for monotherapy and from 1.15 CI95% (0.65, 2.02) to 0.94 CI95% (0.51, 1.74) for polytherapy (see tables 1 and 2 below).
These changes do not modify the conclusions of the study below.

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[2] http://017c85b.netsolhost.com//wp-content/uploads/2013/10/Using_the_Pharmacoepi_Toolbox_in_SAS_2.4.15.pdf

10 RESULTS

10.1 Participants

The current analysis includes a total of 110,336 patients "AED Monotherapy" and 96,215 patients "AED Polytherapy" addressing the study selection criteria found in section 9.4.2. The two patients flow charts below present the number of patients excluded at each stage of the patient selection for Monotherapy and Polytherapy analyses.

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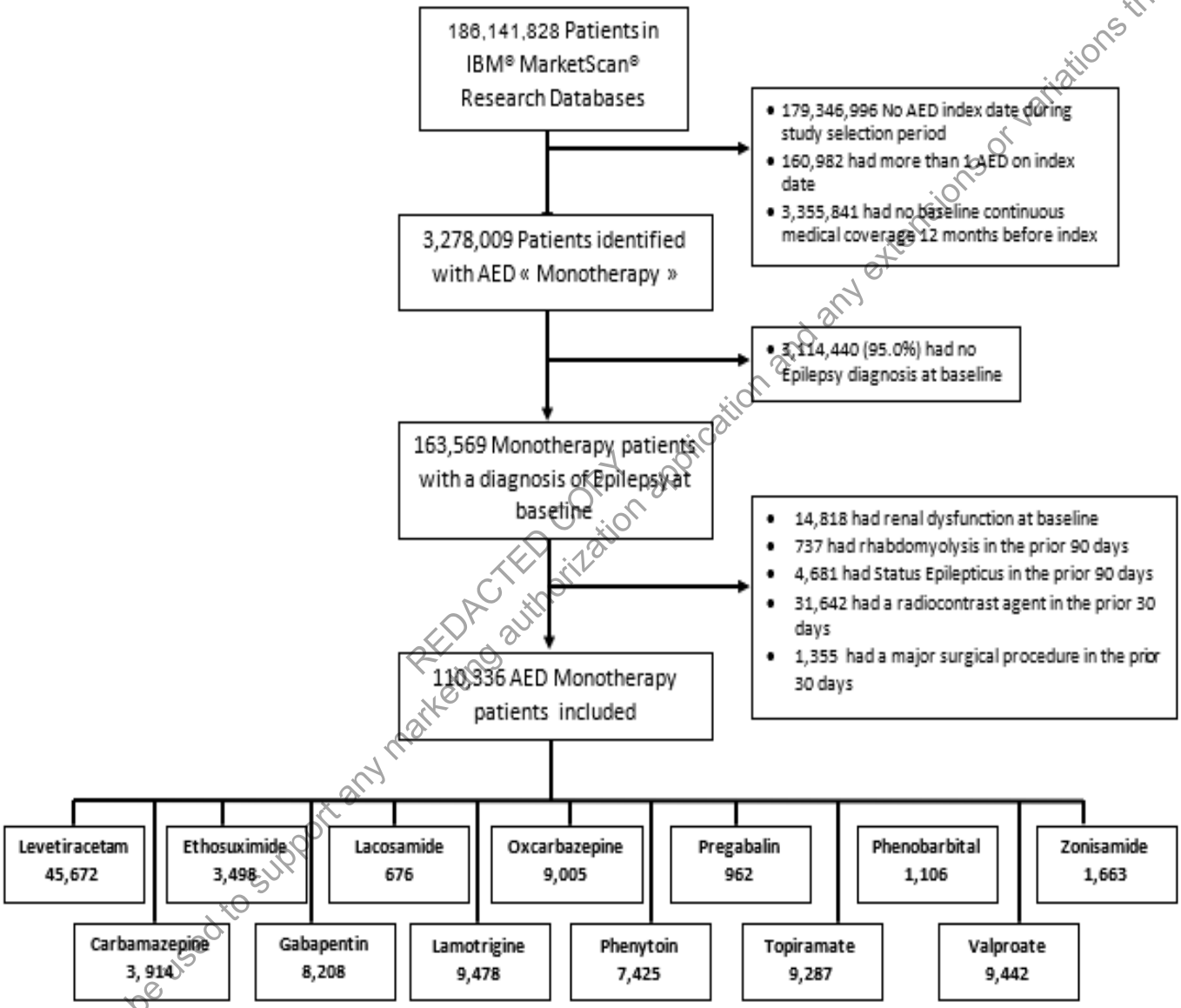
Figure 1. Patient Flow chart: AED "Monotherapy" analysis



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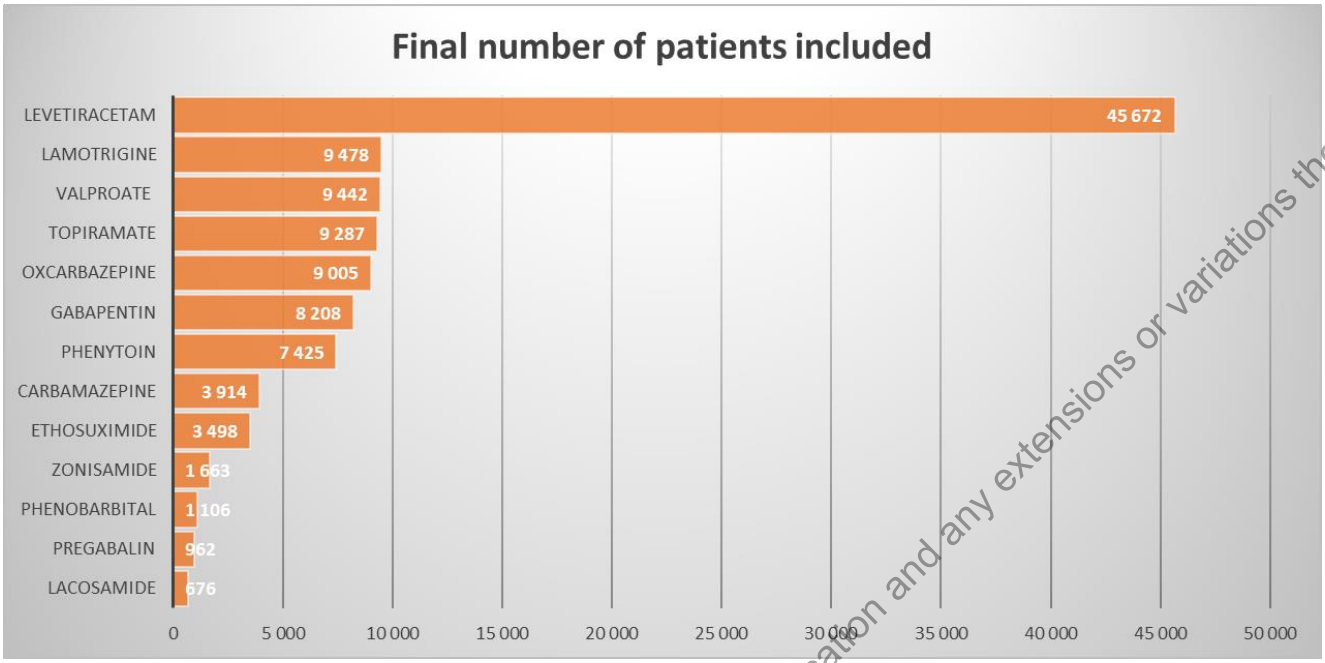

Figure 2 Final number of patients included (Monotherapy analysis)

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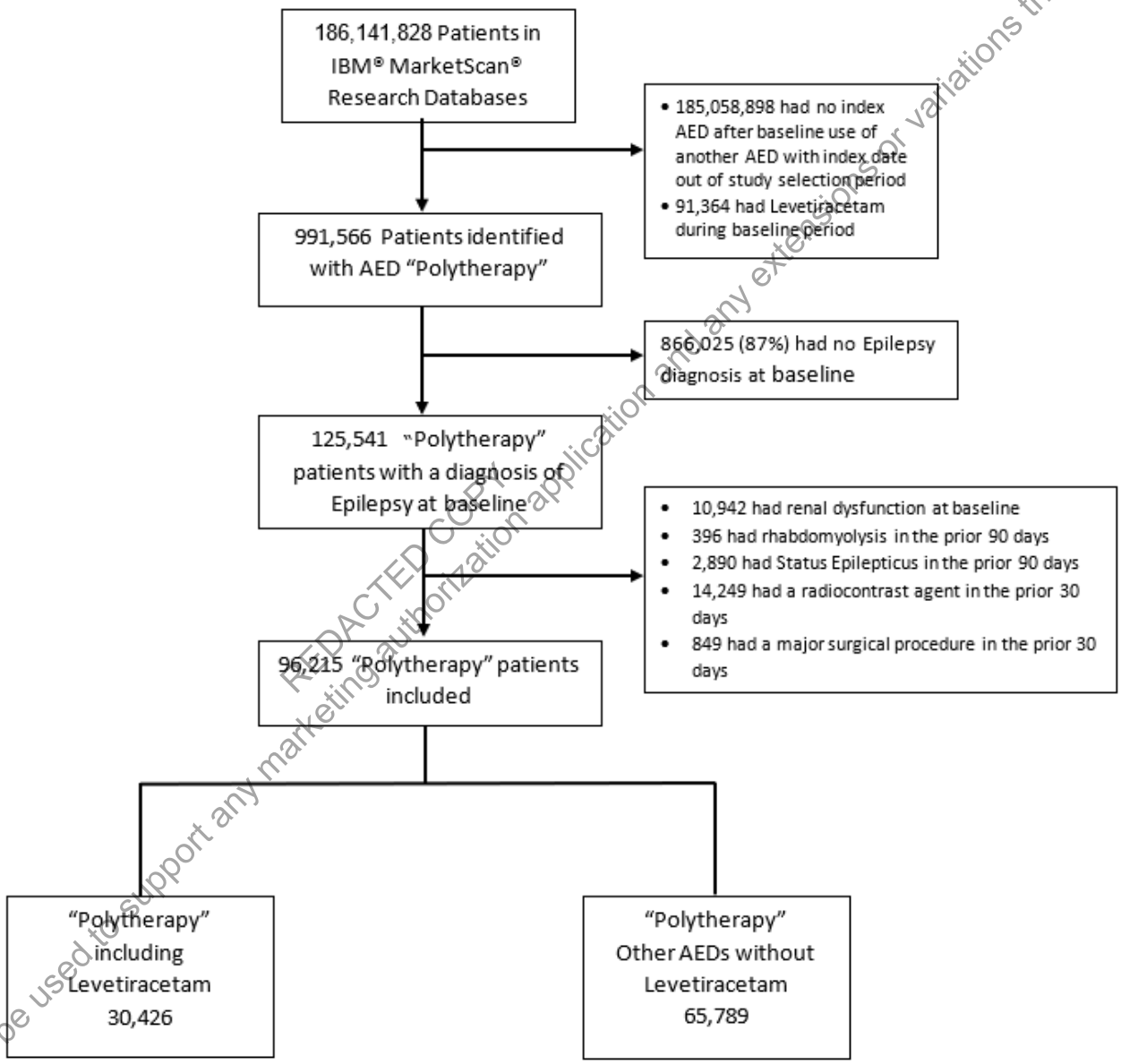
Figure 3 Patient Flow chart: AED "Polytherapy" analysis



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10.2 Patients descriptive characteristics

Data for characteristics of study participants before weighting.

10.2.1 Follow-up

Table 5 and Table 6 show patient's follow-up during the study for the primary analysis. While 98% of patients reached 30 days in the analysis after index, around 2% of patients were censored before reaching this time. In the primary analysis, all patients were included and contributed to the denominator of the incidence rate.

Table 5 Follow-up time in the "Monotherapy" analysis N=110,336.

End of risk period reason:		Overall N= 110,336	LEV N= 45,672	OTH N= 64,664	CBZ N= 3,914	ESX N= 3,498	GBP N= 8,208	LCM N= 676	LTG N= 9,478	OXC N= 9,005	PGB N= 962	PHB N= 1,106	PHT N= 7,425	TPM N= 9,287	VPA N= 9,442	ZNS N= 1,663
Patients had ARF during risk time-window	n(%)	66 (0.1)	39 (0.1)	27 (0.0)	2 (0.1)	0 (0.0)	9 (0.1)	0 (0.0)	1 (0.0)	1 (0.0)	1 (0.1)	0 (0.0)	5 (0.1)	5 (0.1)	3 (0.0)	0 (0.0)
Patients censored before reaching max risk-time window	n(%)	2,477 (2.2)	1,021 (2.2)	1,456 (2.3)	95 (2.4)	64 (1.8)	186 (2.3)	16 (2.4)	218 (2.3)	181 (2.0)	30 (3.1)	30 (2.7)	193 (2.6)	204 (2.2)	198 (2.1)	41 (2.5)
Patients reaching max risk-time window (30 days)	n(%)	107,793 (97.7)	44,612 (97.7)	63,181 (97.7)	3,817 (97.5)	3,434 (98.2)	8,013 (97.6)	660 (97.6)	9,259 (97.7)	8,823 (98.0)	931 (96.8)	1,076 (97.3)	7,227 (97.3)	9,078 (97.7)	9,241 (97.9)	1,622 (97.5)

ARF=Acute renal failure
LEV=Levetiracetam, OTH=All other AEDs, CBZ=Carbamazepine, ESX=Ethosuximide, GBP=Gabapentin, LCM=Lacosamide, LTG=Lamotrigine, OXC=Oxcarbazepine, PGB=Pregabalin, PHB=Phenobarbital, PHT=Phenytoin, TPM=Topiramate, VPA=Valproic acid, ZNS=Zonisamide

Table 6 Follow-up time the "Polytherapy" analysis. N= 96,215.

End of risk period reason:		Overall N=96,215	Polytherapy with Levetiracetam N=30,426	Polytherapy Comparator N=65,789
Patients had ARF during risk time-window	n(%)	63 (0.1)	22 (0.1)	41 (0.1)
Patients censored before reaching max risk-time window	n(%)	2,140 (2.2)	696 (2.3)	1,444 (2.2)
Patients reaching max risk-time window (30 days)	n(%)	94,012 (97.7)	29,708 (97.6)	64,304 (97.7)

ARF=Acute renal failure

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10.2.2 Monotherapy analysis (unweighted)

Descriptive characteristics of patients included in "Monotherapy" analysis are presented below in Table 7, Table 8, Table 9, and

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Table **10** below before weighting.

Substantial differences in age means and age distributions can be observed between each individual AED patient groups. For instance, the mean age of LEV users is 30.3 years while the mean age of OXC users is 14 years old. The use of other drugs (non-AED) drugs at baseline also show substantial differences before weighting. For instance, 15.2% of LEV users also used antidepressants at baseline vs. 25.2% for VPA users and 32.4% for TPM users.

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Table 7 Basic demographic characteristics at baseline for patients included in the "Monotherapy" analysis N=110,336.

		Overall N=110,336	LEV N=45,672	OTH N=64,664	CBZ N=3,914	ESX N=3,498	GBP N=8,208	LCM N=676	LTG N=9,478	OXC N=9,005	PGB N=962	PHB N=1,106	PHT N=7,425	TPM N=9,287	VPA N=9,442	ZNS N=1,663
Gender																
Female	n(%)	57,403(52.0)	22,675(49.6)	34,728(53.7)	1,825(46.6)	2,093(59.8)	4,903(59.7)	392(58.0)	5,801(61.2)	4,027(44.7)	623(64.8)	553(50.0)	3,237(43.6)	6,712(72.3)	3,668(38.8)	894(53.8)
Male	n(%)	52,933(48.0)	22,997(50.4)	29,936(46.3)	2,089(53.4)	1,405(40.2)	3,305(40.3)	284(42.0)	3,677(38.8)	4,978(55.3)	339(35.2)	553(50.0)	4,188(56.4)	2,575(27.7)	5,774(61.2)	769(46.2)
Age (years)	Mean(SD)	29.9(23.48)	30 3(25.76)	29.7(21.72)	30 2(20.60)	8.2(4.39)	44 9(19.12)	41.1(21.88)	27.6(18.61)	14.0(14.95)	49.5(16.84)	30.5(24.85)	46.4(20.83)	28.6(16.50)	27.3(21.75)	23.7(18.24)
	Median(IQR)	22.0(38.00)	20 0(42.00)	24 0(35.00)	28 0(36.00)	8.0(4.00)	47 0(26.50)	39.0(34.00)	22.0(24.00)	9.0(9.00)	51.0(22.00)	31.0(48.00)	47.0(30.00)	26.0(25.00)	19.0(29.00)	17.0(25.00)
	Q1 - Q3	10-48	9-51	11-46	11-47	6-10	31-58	23-57	14-38	6-15	38-60	4-52	30-60	16-41	11-40	10-35
Age groups (years)																
01-03	n(%)	7,709(7.0)	5,087(11.1)	2,622(4.1)	211(5.4)	137(3.9)	84(1.0)	10(1.5)	176(1.9)	1,056(11.7)	1(0.1)	274(24.8)	64(0.9)	207(2.2)	296(3.1)	106(6.4)
04-17	n(%)	37,989(34.4)	15,056(33.0)	22,933(35.5)	1,194(30.5)	3,307(94.5)	638(7.8)	69(10.2)	3,260(34.4)	6,240(69.3)	29(3.0)	176(15.9)	452(6.1)	2,817(30.3)	4,018(42.6)	733(44.1)
18-45	n(%)	34,640(31.4)	12,303(26.9)	22,337(34.5)	1,483(37.9)	44(1.3)	3,183(38.8)	319(47.2)	4,294(45.3)	1,108(12.3)	344(35.8)	265(24.0)	2,996(40.4)	4,568(49.2)	3,149(33.4)	584(35.1)
46-64	n(%)	19,876(18.0)	7,364(16.1)	12,512(19.3)	851(21.7)	9(0.3)	3,277(39.9)	174(25.7)	1,337(14.1)	452(5.0)	443(46.0)	314(28.4)	2,655(35.8)	1,552(16.7)	1,254(13.3)	194(11.7)
65+	n(%)	10,122(9.2)	5,862(12.8)	4,260(6.6)	175(4.5)	1(0.0)	1,026(12.5)	104(15.4)	411(4.3)	149(1.7)	145(15.1)	77(7.0)	1,258(16.9)	143(1.5)	725(7.7)	46(2.8)
Database																
CCAE/MDCR	n(%)	70,250(63.7)	29,487(64.6)	40,763(63.0)	2,421(61.9)	2,126(60.8)	5,124(62.4)	517(76.5)	6,677(70.4)	5,146(57.1)	806(83.8)	644(58.2)	4,721(63.6)	5,934(63.9)	5,548(58.8)	1,099(66.1)
MDCD	n(%)	40,086(36.3)	16,185(35.4)	23,901(37.0)	1,493(38.1)	1,372(39.2)	3,084(37.6)	159(23.5)	2,801(29.6)	3,859(42.9)	156(16.2)	462(41.8)	2,704(36.4)	3,353(36.1)	3,894(41.2)	564(33.9)
Region of employee residence																
North Central	n(%)	16,754(15.2)	7,227(15.8)	9,527(14.7)	610(15.6)	511(14.6)	1,144(13.9)	110(16.3)	1,487(15.7)	1,262(14.0)	173(18.0)	133(12.0)	1,160(15.6)	1,263(13.6)	1,469(15.6)	205(12.3)
Northeast	n(%)	12,963(11.7)	5,777(12.6)	7,186(11.1)	435(11.1)	415(11.9)	1,042(12.7)	82(12.1)	1,221(12.9)	915(10.2)	149(15.5)	114(10.3)	576(7.8)	1,104(11.9)	992(10.5)	141(8.5)
South	n(%)	27,468(24.9)	10,925(23.9)	16,543(25.6)	937(23.9)	800(22.9)	2,037(24.8)	226(33.4)	2,552(26.9)	2,158(24.0)	371(38.6)	259(23.4)	1,951(26.3)	2,601(28.0)	2,104(22.3)	547(32.9)
West	n(%)	12,184(11.0)	5,228(11.4)	6,956(10.8)	405(10.3)	357(10.2)	838(10.2)	92(13.6)	1,334(14.1)	740(8.2)	104(10.8)	130(11.8)	975(13.1)	876(9.4)	911(9.6)	194(11.7)
Unknown	n(%)	40,967(37.1)	16,515(36.2)	24,452(37.8)	1,527(39.0)	1,415(40.5)	3,147(38.3)	166(24.6)	2,884(30.4)	3,930(43.6)	165(17.2)	470(42.5)	2,763(37.2)	3,443(37.1)	3,966(42.0)	576(34.6)
Type of benefit plan																
CDHP	n(%)	4,309(3.9)	1,921(4.2)	2,388(3.7)	129(3.3)	185(5.3)	299(3.6)	32(4.7)	425(4.5)	354(3.9)	29(3.0)	17(1.5)	171(2.3)	383(4.1)	284(3.0)	80(4.8)
Comprehensive	n(%)	23,795(21.6)	10,174(22.3)	13,621(21.1)	915(23.4)	479(13.7)	1,919(23.4)	177(26.2)	1,668(17.6)	1,665(18.5)	197(20.5)	279(25.2)	2,061(27.8)	1,588(17.1)	2,377(25.2)	296(17.8)
EPO	n(%)	759(0.7)	284(0.6)	475(0.7)	24(0.6)	29(0.8)	48(0.6)	3(0.4)	70(0.7)	79(0.9)	16(1.7)	10(0.9)	40(0.5)	90(1.0)	55(0.6)	11(0.7)
HDHP	n(%)	2,726(2.5)	1,215(2.7)	1,511(2.3)	92(2.4)	137(3.9)	160(1.9)	20(3.0)	259(2.7)	238(2.6)	18(1.9)	16(1.4)	89(1.2)	209(2.3)	205(2.2)	68(4.1)
HMO	n(%)	28,741(26.0)	12,278(26.9)	16,463(25.5)	886(22.6)	1,164(33.3)	2,155(26.3)	81(12.0)	2,099(22.1)	2,779(30.9)	117(12.2)	255(23.1)	1,561(21.0)	2,494(26.9)	2,473(26.2)	399(24.0)
POS	n(%)	4,502(4.1)	1,835(4.0)	2,667(4.1)	140(3.6)	124(3.5)	298(3.6)	34(5.0)	474(5.0)	346(3.8)	53(5.5)	39(3.5)	308(4.1)	418(4.5)	354(3.7)	79(4.8)
POS with Capitation	n(%)	1,934(1.8)	635(1.4)	1,299(2.0)	88(2.2)	42(1.2)	151(1.8)	4(0.6)	114(1.2)	149(1.7)	16(1.7)	45(4.1)	304(4.1)	155(1.7)	212(2.2)	19(1.1)
PPO	n(%)	40,471(36.7)	16,238(35.6)	24,233(37.5)	1,477(37.7)	1,248(35.7)	2,953(36.0)	316(46.7)	4,014(42.4)	3,154(35.0)	489(50.8)	408(36.9)	2,660(35.8)	3,626(39.0)	3,223(34.1)	665(40.0)
Unknown	n(%)	3,099(2.8)	1,092(2.4)	2,007(3.1)	163(4.2)	90(2.6)	225(2.7)	9(1.3)	355(3.7)	241(2.7)	27(2.8)	37(3.3)	231(3.1)	324(3.5)	259(2.7)	46(2.8)

LEV=Levetiracetam, OTH=All other AEDs, CBZ=Carbamazepine, ESX=Ethosuximide, GBP=Gabapentin, LCM=Lacosamide, LTG=Lamotrigine, OXC=Oxcarbazepine, PGB=Pregabalin, PHB=Phenobarbital, PHT=Phenytoin, TPM=Topiramate, VPA=Valproic acid, ZNS=Zonisamide
SD=Standard deviation; IQR=Interquartile range;
CCAE/MDCR= IBM MarketScan® Commercial Database / IBM MarketScan® Medicare Supplemental Database; MDCD=IBM MarketScan® Multi-State Medicaid Database;
CDHP=Consumer-Driven Health Plan; EPO=Exclusive Provider Organization Plan; HDHP=High-Deductible Health Plan; HMO=Health Maintenance Organization Plan; POS=Point-of-Service Plan;
PPO=Preferred Provider Organization Plan

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Table 8 Description of comorbidities at baseline in patients included in the "Monotherapy" analysis N=110,336. All ICD-codes used for these conditions can be found in Appendix 3 of the Protocol V1.0

		Overall N=110,336	LEV N=45,672	OTH N=64,664	CBZ N=3,914	ESX N=3,498	GBP N=8,208	LCM N=676	LTG N=9,478	OXC N=9,005	PGB N=962	PHB N=1,106	PHT N=7,425	TPM N=9,287	VPA N=9,442	ZNS N=1,663
Number of comorbidities	Mean(SD)	0.3(0.71)	0.3(0.76)	0.3(0.66)	0.2(0.55)	0.0(0.19)	0.6(0.93)	0.5(0.89)	0.2(0.51)	0.1(0.39)	0.7(0.97)	0.2(0.53)	0.5(0.83)	0.2(0.55)	0.2(0.64)	0.2(0.46)
	Median(IQR)	0.0(0.0)	0.0(0.0)	0.0(0.0)	0.0(0.0)	0.0(0.0)	0.0(1.0)	0.0(1.0)	0.0(0.0)	0.0(0.0)	0.0(1.0)	0.0(0.0)	0.0(1.0)	0.0(0.0)	0.0(0.0)	0.0(0.0)
Any comorbidities	n(%)	23,349(21.2)	10,445(22.9)	12,904(20.0)	631(16.1)	102(2.9)	3,436(41 9)	204(30.2)	1,278(13.5)	818(9.1)	440(45.7)	191(17.3)	2,257(30.4)	1,697(18.3)	1,637(17.3)	213(12.8)
Burns	n(%)	188(0.2)	72(0.2)	116(0.2)	6(0.2)	4(0.1)	26(0.3)	1(0.1)	10(0.1)	16(0.2)	2(0.2)	3(0.3)	9(0.1)	17(0.2)	18(0.2)	4(0.2)
Cardiovascular Disease	n(%)	2,234(2.0)	1,118(2.4)	1,116(1.7)	46(1.2)	1(0.0)	368(4.5)	18(2.7)	99(1.0)	31(0.3)	55(5.7)	7(0.6)	241(3.2)	84(0.9)	157(1.7)	9(0.5)
Cerebrovascular Disease	n(%)	7,558(6.8)	4,232(9.3)	3,326(5.1)	125(3.2)	5(0.1)	875(10.7)	91(13.5)	306(3.2)	188(2.1)	102(10.6)	24(2.2)	764(10.3)	369(4.0)	437(4.6)	40(2.4)
Chronic Obstructive Pulmonary Disease	n(%)	1,937(1.8)	798(1.7)	1,139(1.8)	41(1.0)	1(0.0)	369(4.5)	12(1.8)	87(0.9)	55(0.6)	49(5.1)	31(2.8)	253(3.4)	104(1.1)	127(1.3)	10(0.6)
Diabetes Mellitus	n(%)	5,174(4.7)	2,214(4.8)	2,960(4.6)	141(3.6)	6(0.2)	983(12 0)	45(6.7)	255(2.7)	132(1.5)	140(14.6)	29(2.6)	500(6.7)	339(3.7)	347(3.7)	43(2.6)
Diabetic Nephropathy	n(%)	49(0.0)	30(0.1)	19(0.0)	2(0.1)	0(0.0)	8(0.1)	0(0.0)	1(0.0)	0(0 0)	0(0.0)	0(0.0)	1(0.0)	3(0.0)	2(0.0)	2(0.1)
Heart Failure	n(%)	752(0.7)	432(0.9)	320(0.5)	10(0.3)	0(0.0)	113(1.4)	4(0.6)	27(0.3)	1(0 0)	13(1.4)	7(0.6)	83(1.1)	19(0.2)	40(0.4)	3(0.2)
Hemolysis	n(%)	2(0.0)	1(0.0)	1(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0 0)	0(0.0)	0(0.0)	1(0.0)	0(0.0)	0(0.0)	0(0.0)
Hypertension	n(%)	8,656(7.8)	3,878(8.5)	4,778(7.4)	251(6.4)	6(0.2)	1,390(16 9)	77(11.4)	397(4.2)	172(1.9)	176(18.3)	64(5.8)	1,008(13.6)	579(6.2)	597(6.3)	61(3.7)
Hypotension	n(%)	386(0.3)	171(0.4)	215(0.3)	7(0.2)	0(0.0)	67(0.8)	2(0.3)	23(0.2)	6(0.1)	7(0.7)	0(0.0)	40(0.5)	28(0.3)	33(0.3)	2(0.1)
Hypovolaemia	n(%)	591(0.5)	274(0.6)	317(0.5)	16(0.4)	1(0.0)	61(0.7)	3(0.4)	29(0.3)	50(0.6)	13(1.4)	9(0.8)	48(0.6)	39(0.4)	42(0.4)	6(0.4)
Liver Disease	n(%)	503(0.5)	220(0.5)	283(0.4)	6(0.2)	0(0.0)	116(1.4)	4(0.6)	23(0.2)	9(0.1)	7(0.7)	2(0.2)	38(0.5)	41(0.4)	27(0.3)	10(0.6)
Myoglobinuria	n(%)	1(0.0)	1(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0 0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Obesity	n(%)	481(0.4)	144(0.3)	337(0.5)	11(0.3)	14(0.4)	55(0.7)	2(0.3)	44(0.5)	26(0.3)	9(0.9)	3(0.3)	36(0.5)	105(1.1)	25(0.3)	7(0.4)
Other Renal Diseases	n(%)	3,583(3.2)	1,378(3.0)	2,205(3.4)	115(2.9)	65(1.9)	436(5.3)	42(6.2)	275(2.9)	271(3.0)	63(6.5)	39(3.5)	199(2.7)	311(3.3)	333(3.5)	56(3.4)
Peripheral Vascular Disease	n(%)	772(0.7)	368(0.8)	404(0.6)	14(0.4)	2(0.1)	144(1.8)	11(1.6)	29(0.3)	13(0.1)	19(2.0)	3(0.3)	74(1.0)	28(0.3)	66(0.7)	1(0.1)
Proteinuria	n(%)	39(0.0)	12(0.0)	27(0.0)	1(0.0)	2(0.1)	5(0.1)	0(0.0)	5(0.1)	2(0 0)	0(0.0)	0(0.0)	3(0.0)	3(0.0)	5(0.1)	1(0.1)
Renal Calculi	n(%)	502(0.5)	154(0.3)	348(0.5)	18(0.5)	1(0.0)	110(1.3)	8(1.2)	48(0.5)	18(0.2)	14(1.5)	5(0.5)	32(0.4)	53(0.6)	36(0.4)	5(0.3)
Sepsis	n(%)	795(0.7)	422(0.9)	373(0.6)	14(0.4)	0(0.0)	107(1.3)	7(1.0)	28(0.3)	16(0.2)	9(0.9)	15(1.4)	91(1.2)	21(0.2)	61(0.6)	4(0.2)
Small Kidney Of Unknown Cause	n(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0 0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Systemic Lupus Erythematosus	n(%)	176(0.2)	66(0.1)	110(0.2)	7(0.2)	0(0.0)	46(0.6)	2(0.3)	10(0.1)	2(0 0)	4(0.4)	2(0.2)	5(0.1)	24(0.3)	7(0.1)	1(0.1)

LEV=Levetiracetam, OTH=All other AEDs, CBZ=Carbamazepine, ESX=Ethosuximide, GBP=Gabapentin, LCM=Lacosamide, LTG=Lamotrigine, OXC=Oxcarbazepine, PGB=Pregabalin, PHB=Phenobarbital, PHT=Phenytoin, TPM=Topiramate, VPA=Valproic acid, ZNS=Zonisamide
SD=Standard deviation; IQR=Interquartile range

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Table 9 Description of drug use by drug classes at baseline in patients included in the "Monotherapy" analysis (N=110,336).

		Overall N=110,336	LEV N=45,672	OTH N=64,664	CBZ N=3,914	ESX N=3,498	GBP N=8,208	LCM N=676	LTG N=9,478	OXC N=9,005	PGB N=962	PHB N=1,106	PHT N=7,425	TPM N=9,287	VPA N=9,442	ZNS N=1,663
Any non-AED	n(%)	94,273(85.4)	38,949(85.3)	55,324(85.6)	3,067(78.4)	2,659(76 0)	7,891(96.1)	543(80.3)	8,045(84.9)	7,535(83.7)	927(96.4)	842(76.1)	5,973(80.4)	8,569(92.3)	7,854(83.2)	1,419(85.3)
Analgesics	n(%)	38,446(34.8)	13,885(30.4)	24,561(38.0)	1,168(29.8)	302(8.6)	5,732(69.8)	231(34.2)	2,976(31.4)	1,674(18.6)	727(75.6)	284(25.7)	3,088(41.6)	4,812(51.8)	3,051(32.3)	516(31.0)
Antidepressants	n(%)	22,578(20.5)	6,926(15.2)	15,652(24.2)	598(15.3)	52(1.5)	3,406(41.5)	147(21.7)	2,636(27.8)	1,005(11.2)	393(40.9)	113(10.2)	1,628(21.9)	3,011(32.4)	2,378(25.2)	285(17.1)
Antimicrobials And Antiviral Drugs	n(%)	53,073(48.1)	21,842(47.8)	31,231(48.3)	1,616(41.3)	1,684(48.1)	4,739(57.7)	275(40.7)	4,344(45.8)	4,568(50.7)	549(57.1)	485(43.9)	2,889(38.9)	5,164(55.6)	4,132(43.8)	786(47.3)
Antineoplastics	n(%)	272(0.2)	127(0.3)	145(0.2)	9(0.2)	1(0 0)	51(0.6)	6(0.9)	20(0.2)	6(0.1)	7(0.7)	1(0.1)	17(0.2)	16(0.2)	11(0.1)	0(0.0)
Antipsychotics	n(%)	6,138(5.6)	1,446(3.2)	4,692(7.3)	230(5.9)	32(0.9)	682(8.3)	32(4.7)	794(8.4)	477(5.3)	61(6.3)	38(3.4)	437(5.9)	464(5.0)	1,373(14.5)	72(4.3)
Benzodiazepines	n(%)	16,214(14.7)	6,710(14.7)	9,504(14.7)	428(10.9)	116(3.3)	1,863(22.7)	91(13.5)	1,288(13.6)	1,801(20.0)	262(27.2)	111(10.0)	793(10.7)	1,341(14.4)	1,127(11.9)	283(17.0)
Cardiovascular Drugs	n(%)	16,726(15.2)	7,553(16.5)	9,173(14.2)	421(10.8)	8(0 2)	2,551(31.1)	143(21.2)	910(9.6)	341(3.8)	345(35.9)	115(10.4)	1,715(23.1)	1,360(14.6)	1,126(11.9)	138(8.3)
Immunosuppressants	n(%)	516(0.5)	214(0.5)	302(0.5)	20(0.5)	9(0 3)	92(1.1)	3(0.4)	41(0.4)	21(0.2)	15(1.6)	6(0.5)	20(0.3)	50(0.5)	20(0.2)	5(0.3)
Methotrexate	n(%)	354(0.3)	165(0.4)	189(0.3)	3(0.1)	3(0.1)	60(0.7)	2(0.3)	23(0.2)	7(0.1)	18(1.9)	7(0.6)	20(0.3)	27(0.3)	15(0.2)	4(0.2)
Other Drugs	n(%)	15,021(13.6)	5,994(13.1)	9,027(14.0)	394(10.1)	59(1.7)	2,243(27.3)	128(18.9)	1,168(12.3)	643(7.1)	309(32.1)	122(11.0)	1,138(15.3)	1,524(16.4)	1,127(11.9)	172(10.3)
Steroids	n(%)	23,943(21.7)	9,724(21.3)	14,219(22.0)	671(17.1)	624(17.8)	2,773(33.8)	127(18.8)	1,721(18.2)	1,850(20.5)	356(37.0)	206(18.6)	1,254(16.9)	2,578(27.8)	1,713(18.1)	346(20.8)

AED=Antiepileptic drug
LEV=Levetiracetam, OTH=All other AEDs, CBZ=Carbamazepine, ESX=Ethosuximide, GBP=Gabapentin, LCM=Lacosamide, LTG=Lamotrigine, OXC=Oxcarbazepine, PGB=Pregabalin, PHB=Phenobarbital, PHT=Phenytoin, TPM=Topiramate, VPA=Valproic acid, ZNS=Zonisamide

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Table 10 Health services utilization in patients included in the "Monotherapy" analysis (N=110,336).

		Overall N=49586	LEV N=45,672	OTH N=64,664	CBZ N=3,914	ESX N=3,498	GBP N=8,208	LCM N=676	LTG N=9,478	OXC N=9,005	PGB N=962	PHB N=1,106	PHT N=7,425	TPM N=9,287	VPA N=9,442	ZNS N=1,663
All cause																
Overall outpatient visits	n(%)	107,461(97.4)	44,274(96.9)	63,187(97.7)	3,797(97.0)	3,493(99.9)	8,123(99.0)	664(98.2)	9,369(98 8)	8,870(98.5)	956(99.4)	1,070(96.7)	6,809(91.7)	9,180(98.8)	9,217(97.6)	1,639(98.6)
Hospitalizations	n(%)	31,762(28 8)	14,877(32.6)	16,885(26.1)	823(21.0)	142(4.1)	3,428(41.8)	218(32.2)	1,921(20 3)	1,954(21.7)	385(40.0)	340(30.7)	2,803(37.8)	1,850(19.9)	2,703(28.6)	318(19.1)
ED visits	n(%)	70,459(63 9)	31,337(68.6)	39,122(60.5)	2,116(54.1)	1,081(30.9)	5,398(65.8)	380(56.2)	5,536(58.4)	5,875(65.2)	578(60.1)	604(54.6)	4,813(64.8)	5,870(63.2)	5,813(61.6)	1,058(63.6)
Epilepsy related																
Overall outpatient visits	n(%)	65,167(59.1)	25,299(55.4)	39,868(61.7)	2,522(64.4)	2,902(83.0)	3,911(47.6)	493(72.9)	7,047(74.4)	6,394(71.0)	556(57.8)	623(56.3)	2,743(36.9)	5,767(62.1)	5,736(60.7)	1,174(70.6)
Hospitalizations	n(%)	11,229(10 2)	6,503(14.2)	4,726(7.3)	259(6.6)	84(2.4)	308(3.8)	99(14.6)	549(5.8)	1,038(11.5)	43(4.5)	90(8.1)	987(13.3)	416(4.5)	719(7.6)	134(8.1)
ED visits	n(%)	38,676(35.1)	19,972(43.7)	18,704(28.9)	1,099(28.1)	310(8.9)	1,440(17.5)	198(29.3)	2,994(31.6)	3,619(40.2)	152(15.8)	308(27.8)	2,998(40.4)	2,189(23.6)	2,796(29.6)	601(36.1)
Non-epilepsy related																
Overall outpatient visits	n(%)	104,646(94.8)	43,142(94.5)	61,504(95.1)	3,644(93.1)	3,381(96.7)	8,084(98.5)	634(93.8)	9,036(95 3)	8,645(96.0)	950(98.8)	1,025(92.7)	6,548(88.2)	9,055(97.5)	8,930(94.6)	1,572(94.5)
Hospitalizations	n(%)	22,872(20.7)	9,812(21.5)	13,060(20.2)	600(15.3)	59(1.7)	3,248(39.6)	141(20.9)	1,449(15 3)	1,012(11.2)	359(37.3)	274(24.8)	2,081(28.0)	1,504(16.2)	2,125(22.5)	208(12.5)
ED visits	n(%)	49,185(44.6)	19,965(43.7)	29,220(45.2)	1,527(39.0)	887(25.4)	4,917(59.9)	272(40.2)	3,703(39.1)	3,707(41.2)	507(52.7)	492(44.5)	3,282(44.2)	4,871(52.4)	4,370(46.3)	685(41.2)

LEV=Levetiracetam, OTH=All other AEDs, CBZ=Carbamazepine, ESX=Ethosuximide, GBP=Gabapentin, LCM=Lacosamide, LTG=Lamotrigine, OXC=Oxcarbazepine, PGB=Pregabalin, PHB=Phenobarbital, PHT=Phenytoin, TPM=Topiramate, VPA=Valproic acid, ZNS=Zonisamide;
ED=Emergency department

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10.2.3 Polytherapy analysis (unweighted)

Below in Table 11, Table 12, and Table 13, the characteristics of patients included in the "polytherapy" analysis, levetiracetam and comparator group. In this analysis, before weighting, the mean age of both groups was already more similar (mean of 36.8 years for polytherapy with levetiracetam vs. 35.8 years for polytherapy without levetiracetam) although the LEV group is more represented in the younger and older age group than the comparator group.

Table 11 Basic demographic characteristics for patients included in the "polytherapy" analysis. N= 96,215

		Overall N=96,215	Polytherapy with Levetiracetam N=30,426	Polytherapy Comparator N=65,789
Gender				
Female	n(%)	55,563(57.7)	16,621(54.6)	38,942(59.2)
Male	n(%)	40,652(42.3)	13,805(45.4)	26,847(40.8)
Age (years)	Mean(SD)	36.1(20.43)	36.8(22.19)	35.8(19.56)
	Median(IQR)	35.0(33.00)	35.0(36.00)	35.0(32.00)
	Q1 - Q3	19-52	18-54	19-51
Age groups (years)				
01-03	n(%)	1,999(2.1)	1,127(3.7)	872(1.3)
04-17	n(%)	20,097(20.9)	6,235(20.5)	13,862(21.1)
18-45	n(%)	40,459(42.1)	11,781(38.7)	28,678(43.6)
46-64	n(%)	26,395(27.4)	8,012(26.3)	18,383(27.9)
65+	n(%)	7,265(7.6)	3,271(10.8)	3,994(6.1)
Database				
CCAE/MDCR	n(%)	58,211(60.5)	19,572(64.3)	38,639(58.7)
MDCD	n(%)	38,004(39.5)	10,854(35.7)	27,150(41.3)
Region of employee residence				
North Central	n(%)	14,135(14.7)	4,829(15.9)	9,306(14.1)
Northeast	n(%)	9,913(10.3)	3,376(11.1)	6,537(9.9)
South	n(%)	23,485(24.4)	7,631(25.1)	15,854(24.1)
West	n(%)	9,926(10.3)	3,507(11.5)	6,419(9.8)
Unknown	n(%)	38,756(40.3)	11,083(36.4)	27,673(42.1)
Type of benefit plan				
CDHP	n(%)	3,184(3.3)	1,062(3.5)	2,122(3.2)
Comprehensive	n(%)	23,955(24.9)	7,358(24.2)	16,597(25.2)
EPO	n(%)	664(0.7)	213(0.7)	451(0.7)
HDHP	n(%)	1,700(1.8)	566(1.9)	1,134(1.7)
HMO	n(%)	22,546(23.4)	7,029(23.1)	15,517(23.6)
POS	n(%)	3,810(4.0)	1,301(4.3)	2,509(3.8)
POS with Capitation	n(%)	2,567(2.7)	788(2.6)	1,779(2.7)
PPO	n(%)	34,621(36.0)	11,124(36.6)	23,497(35.7)
Unknown	n(%)	3,168(3.3)	985(3.2)	2,183(3.3)

SD=Standard deviation; IQR=Interquartile range;
CCAE/MDCR= IBM MarketScan® Commercial Database / IBM MarketScan® Medicare Supplemental Database;
MDCD=IBM MarketScan® Multi-State Medicaid Database
CDHP=Consumer-Driven Health Plan; EPO=Exclusive Provider Organization Plan; HDHP=High-Deductible Health Plan; HMO=Health Maintenance Organization Plan; POS=Point-of-Service Plan; PPO=Preferred Provider Organization Plan

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Table 12 Descriptive characteristics of main comorbidities in patients included in the "Polytherapy" analysis N=96,215. All ICD-codes for these conditions can be found in Appendix 3 of the Protocol V1.0

		Overall N=96,215	Polytherapy with Levetiracetam N=30,426	Polytherapy Comparator N=65,789
Number of comorbidities	Mean(SD)	0.4(0.75)	0.4(0.79)	0.4(0.73)
	Median(IQR)	0.0(1.0)	0.0(1.0)	0.0(1.0)
Any comorbidities	n(%)	25,561(26.6)	8,208(27.0)	17,353(26.4)
Burns	n(%)	240(0.2)	77(0.3)	163(0.2)
Cardiovascular Disease	n(%)	2,090(2.2)	740(2.4)	1,350(2.1)
Cerebrovascular Disease	n(%)	5,396(5.6)	2,378(7.8)	3,018(4.6)
Chronic Obstructive Pulmonary Disease	n(%)	2,882(3.0)	791(2.6)	2,091(3.2)
Diabetes Mellitus	n(%)	6,216(6.5)	1,820(6.0)	4,396(6.7)
Diabetic Nephropathy	n(%)	48(0.0)	16(0.1)	32(0.0)
Heart Failure	n(%)	687(0.7)	291(1.0)	396(0.6)
Hemolysis	n(%)	2(0.0)	1(0.0)	1(0.0)
Hypertension	n(%)	9,647(10.0)	3,161(10.4)	6,486(9.9)
Hypotension	n(%)	359(0.4)	121(0.4)	238(0.4)
Hypovolaemia	n(%)	567(0.6)	190(0.6)	377(0.6)
Liver Disease	n(%)	561(0.6)	199(0.7)	362(0.6)
Myoglobinuria	n(%)	2(0.0)	0(0.0)	2(0.0)
Obesity	n(%)	639(0.7)	142(0.5)	497(0.8)
Other Renal Diseases	n(%)	4,630(4.8)	1,372(4.5)	3,258(5.0)
Peripheral Vascular Disease	n(%)	810(0.8)	295(1.0)	515(0.8)
Proteinuria	n(%)	43(0.0)	12(0.0)	31(0.0)
Renal Calculi	n(%)	870(0.9)	274(0.9)	596(0.9)
Sepsis	n(%)	716(0.7)	319(1.0)	397(0.6)
Small Kidney Of Unknown Cause	n(%)	0(0.0)	0(0.0)	0(0.0)
Systemic Lupus Erythematosus	n(%)	314(0.3)	78(0.3)	236(0.4)

SD=Standard deviation; IQR=Interquartile range

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Table 13 Description of drug use (AEDs and non-AEDs) in patients included in the "Polytherapy" analysis N=96,215

		Overall N=96,215	Polytherapy with Levetiracetam N=30,426	Polytherapy Comparator N=65,789
Any prescription	n(%)	96,215(100)	30,426(100)	65,789(100)
Any AED	n(%)	96,215(100)	30,426(100)	65,789(100)
Brivaracetam	n(%)	4(0.0)	1(0.0)	3(0.0)
Carbamazepine	n(%)	10,506(10.9)	3,332(11.0)	7,174(10.9)
Clobazam	n(%)	375(0.4)	75(0.2)	300(0.5)
Clonazepam	n(%)	12,399(12.9)	2,820(9.3)	9,579(14.6)
Eslicarbazepine Acetate	n(%)	65(0.1)	16(0.1)	49(0.1)
Ethosuximide	n(%)	2,497(2.6)	553(1.8)	1,944(3.0)
Ezogabine	n(%)	9(0.0)	1(0.0)	8(0.0)
Felbamate	n(%)	288(0.3)	61(0.2)	227(0.3)
Gabapentin	n(%)	11,196(11.6)	3,395(11.2)	7,801(11.9)
Lacosamide	n(%)	1,303(1.4)	343(1.1)	960(1.5)
Lamotrigine	n(%)	14,483(15.1)	3,918(12.9)	10,565(16.1)
Levetiracetam	n(%)	0(0.0)	0(0.0)	0(0.0)
Oxcarbazepine	n(%)	10,189(10.6)	3,475(11.4)	6,714(10.2)
Perampanel	n(%)	37(0.0)	4(0.0)	33(0.1)
Phenobarbital	n(%)	3,943(4.1)	1,507(5.0)	2,436(3.7)
Phenytoin	n(%)	16,511(17.2)	6,900(22.7)	9,611(14.6)
Pregabalin	n(%)	2,790(2.9)	614(2.0)	2,176(3.3)
Primidone	n(%)	837(0.9)	264(0.9)	573(0.9)
Rufinamide	n(%)	161(0.2)	19(0.1)	142(0.2)
Tiagabine	n(%)	154(0.2)	41(0.1)	113(0.2)
Topiramate	n(%)	13,636(14.2)	3,417(11.2)	10,219(15.5)
Valproic Acid	n(%)	16,226(16.9)	4,707(15.5)	11,519(17.5)
Vigabatrin	n(%)	90(0.1)	37(0.1)	53(0.1)
Zonisamide	n(%)	3,541(3.7)	887(2.9)	2,654(4.0)
Any non-AED	n(%)	90,426(94.0)	28,063(92.2)	62,363(94.8)
Analgesics	n(%)	49,921(51.9)	13,529(44.5)	36,392(55.3)
Antidepressants	n(%)	35,593(37.0)	8,240(27.1)	27,353(41.6)
Antimicrobials and Antiviral Drugs	n(%)	52,989(55.1)	15,931(52.4)	37,058(56.3)
Antineoplastics	n(%)	291(0.3)	113(0.4)	178(0.3)
Antipsychotics	n(%)	13,320(13.8)	2,386(7.8)	10,934(16.6)
Benzodiazepines	n(%)	20,933(21.8)	5,859(19.3)	15,074(22.9)
Cardiovascular Drugs	n(%)	21,717(22.6)	6,852(22.5)	14,865(22.6)
Immunosuppressants	n(%)	648(0.7)	175(0.6)	473(0.7)
Methotrexate	n(%)	538(0.6)	154(0.5)	384(0.6)
Other Drugs	n(%)	21,982(22.8)	6,099(20.0)	15,883(24.1)
Steroids	n(%)	25,903(26.9)	7,289(24.0)	18,614(28.3)

AED=Antiepileptic drug

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10.3 Outcome data

Overall, a very low number of cases of ARFs were found in patients selected for the study using AEDs. Out of the 110,366 patients included in the "Monotherapy" analysis, only 66 ARF cases were found within the first 30 days, increasing to 132 within 60 days and 184 within 90 days from index prescription (see Table 14 below).

The numbers of ARFs for each individual AED user group for the primary analysis are extremely low (Table 15). Although we identified 39 ARFs in the levetiracetam group (45,672 LEV users included), the numbers decrease substantially for gabapentin (9 ARFs for 8,208 gabapentin users), topiramate (5 ARFs for 9,287 topiramate users), phenytoin (5 ARFs for 7,425 phenytoin users), and valproic acid (3 ARFs for 9,442 valproic acid users). All other individual AED groups include two or less ARF cases.

The attrition table (Table 14) shows the number of ARF cases left after applying the inclusion/exclusion criteria to patients in the database for the primary analysis. Having a diagnosis of epilepsy during baseline reduces the number of ARF cases by 88%, followed by the exclusion of patients with codes of renal failures or other renal dysfunction observed during baseline (1 year before index date), reducing the number of ARFs included by 78%. Having a procedure involving the use of a radiocontrast agent within the past 30 days before the index date also reduces substantially the number of ARFs in the sample (51%). Similar findings have been observed for the "Polytherapy" analysis with, of the 96,215 patients included, only 63 ARF cases found within the first 30 days, increasing to 114 within 60 days and 166 within 90 days from index prescription (see Table 16).

Table 14. Number of ARFs in patients selected in the Monotherapy analysis, primary diagnosis

	30 days (Primary)		60 days (Sensitivity)		90 days (Sensitivity)	
In patients with the following inclusion/exclusion criteria	ARF excluded n(%)	ARF included	ARF excluded n(%)	ARF included	ARF excluded n(%)	ARF included
Inclusion: Had epilepsy diagnosis during baseline	5,100 (88%)	710	8,243 (90%)	965	10,923 (90%)	1,219
Exclusion: Had renal dysfunction or renal failure during baseline	556 (78%)	154	682 (71%)	283	823 (68%)	396
Exclusion: Had rhabdomyolysis in the 90 days prior to index date	6 (4%)	148	7 (2%)	276	7 (2%)	389
Exclusion: Had Status Epilepticus in the 90 days prior to index date	7 (5%)	141	12 (4%)	264	23 (6%)	366
Exclusion: Had procedure code using radiocontrast in the 30 days prior to index date	72 (51%)	69	126 (48%)	138	172 (47%)	194
Exclusion: Had major surgical procedure during hospitalization (>24hrs) in the 30 days prior to index date	3 (4%)	**66**	6 (4%)	**132**	10 (5%)	**184**

ARF=Acute renal failure

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Table 15. Number of ARFs included for each AED in the "Monotherapy analysis", primary diagnosis (unweighted)

Comparator group	Number of patients included	30 days (Primary)	60 days (Sensitivity)	90 days (Sensitivity)
Levetiracetam	45,672	**39**	71	91
Carbamazepine	3,914	**2**	4	5
Ethosuximide	3,498	**0**	0	1
Gabapentin	8,208	**9**	22	32
Lacosamide	676	**0**	0	0
Lamotrigine	9,478	**1**	3	5
Oxcarbazepine	9,005	**1**	2	4
Pregabalin	962	**1**	3	3
Phenobarbital	1,106	**0**	1	2
Phenytoin	7,425	**5**	12	21
Topiramate	9,287	**5**	9	11
Valproic acid	9,442	**3**	5	9
Zonisamide	1,663	**0**	0	0
Monotherapy overall (not levetiracetam)	64,664	**27**	61	93

Table 16. Number of ARFs included for each AED in the "Polytherapy analysis", primary diagnosis (unweighted)

	30 days (Primary)		60 days (Sensitivity)		90 days (Sensitivity)	
In patients with the following inclusion/exclusion criteria	ARF excluded n(%)	ARF included	ARF excluded n(%)	ARF included	ARF excluded n(%)	ARF included
Inclusion: Had epilepsy diagnosis during baseline	1,459 (78%)	423	2,479 (80%)	625	3,452 (81%)	816
Exclusion: Had renal dysfunction or renal failure during baseline	318 (75%)	105	444 (71%)	181	559 (69%)	257
Exclusion: Had rhabdomyolysis in the 90 days prior to index date	3 (3%)	102	4 (2%)	177	5 (2%)	252
Exclusion: Had Status Epilepticus in the 90 days prior to index date	4 (4%)	98	10 (6%)	167	12 (5%)	240
Exclusion: Had procedure code using radiocontrast in the 30 days prior to index date	33 (34%)	65	50 (30%)	117	68 (28%)	172
Exclusion: Had major surgical proc edure during hospitalization (>24hrs) in the 30 days prior to index date	2 (3%)	**63**	3 (3%)	**114**	6 (3%)	**166**

ARF=Acute renal failure

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10.4 Main results

As per protocol, analyses with less than 3000 patients or less than 1 ARF case were not performed.

10.4.1 Assessment on model assumptions

In order to assess the adequacy of model assumptions, the following sections present the distributions of propensity score for each analysis arm, distributions of stabilized weight and standardized differences in means for baseline covariates.

10.4.1.1 Propensity score distributions

Below the distributions of unweighted and weighted propensity score (PS) distributions for the primary analysis (30 days with primary ARF diagnosis).

- Monotherapy analysis

  Figure 4, Figure 5, and Figure 6 show the unweighted and weighted PS distributions obtained from HDPS models.

  Distributions of propensity scores show substantial differences for 1:1 comparisons before weighting, especially for oxcarbazepine or gabapentin.

  These distributions show some improvement in overlapping after weighting, nevertheless, region of overlapping is still considered inadequate in most 1:1 comparisons except for the comparison for valproic acid.

  Higher degree of overlapping between LEV and comparator cohorts is found for the Mono-overall comparison, and sufficient overlapping area is observed after weighting.

- Polytherapy analysis

  Polytherapy analysis has similar observations as the Mono-overall comparison described above. Both the LEV polytherapy group and the polytherapy comparator show an adequate degree of overlapping, improved by the weighting. (see Figure 6)

Conclusion: When examining these distributions, we can already foresee issues with the models for 1:1 comparisons, due to marked differences in the populations and relatively low numbers in each of the comparator groups. The absolute standardized differences in means of relevant covariates will help to evaluate the validity of these models further in section 10.4.1.3 below.

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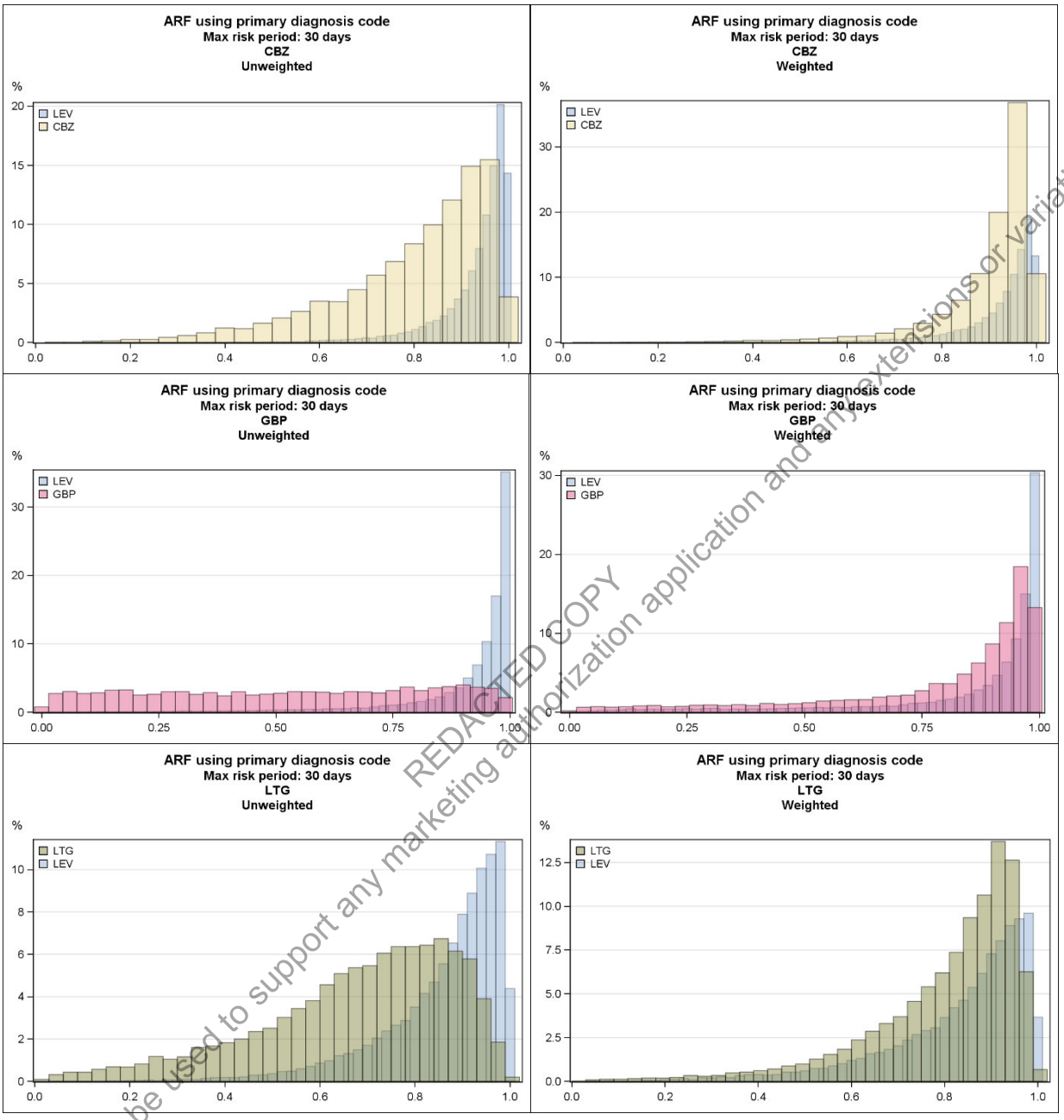

Figure 4 Unweighted and weighted PS distributions for levetiracetam (LEV), carbamazepine (CBZ), gabapentin (GBP) and lamotrigine (LTG). Y-axis shows the percentage of participants, x-axis shows propensity score.

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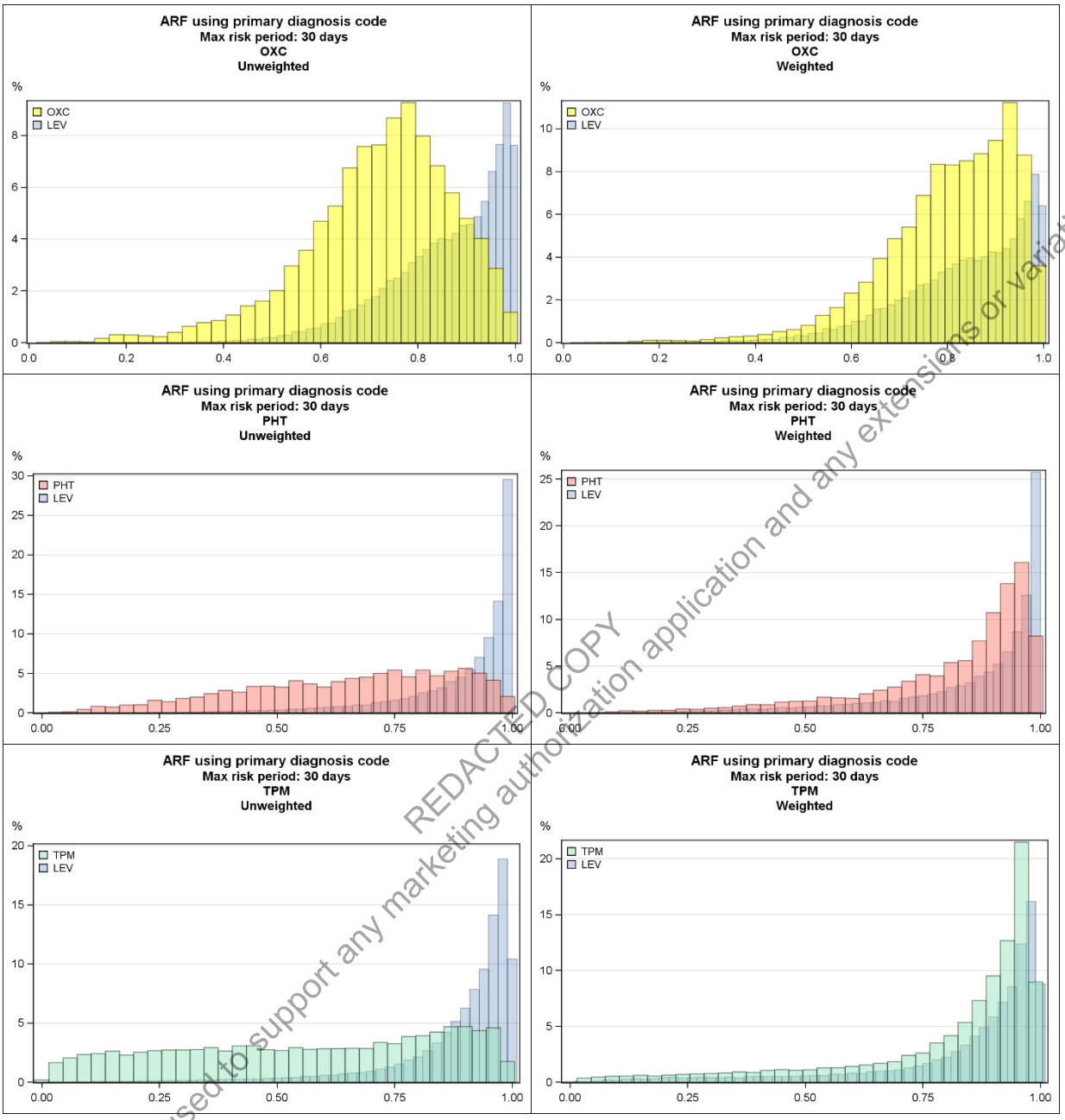

Figure 5 Unweighted and weighted PS distributions for levetiracetam (LEV), oxcarbazepine (OXC), phenytoin (PHT) and topiramate (TPM). Y-axis shows the percentage of participants, x-axis shows propensity score.

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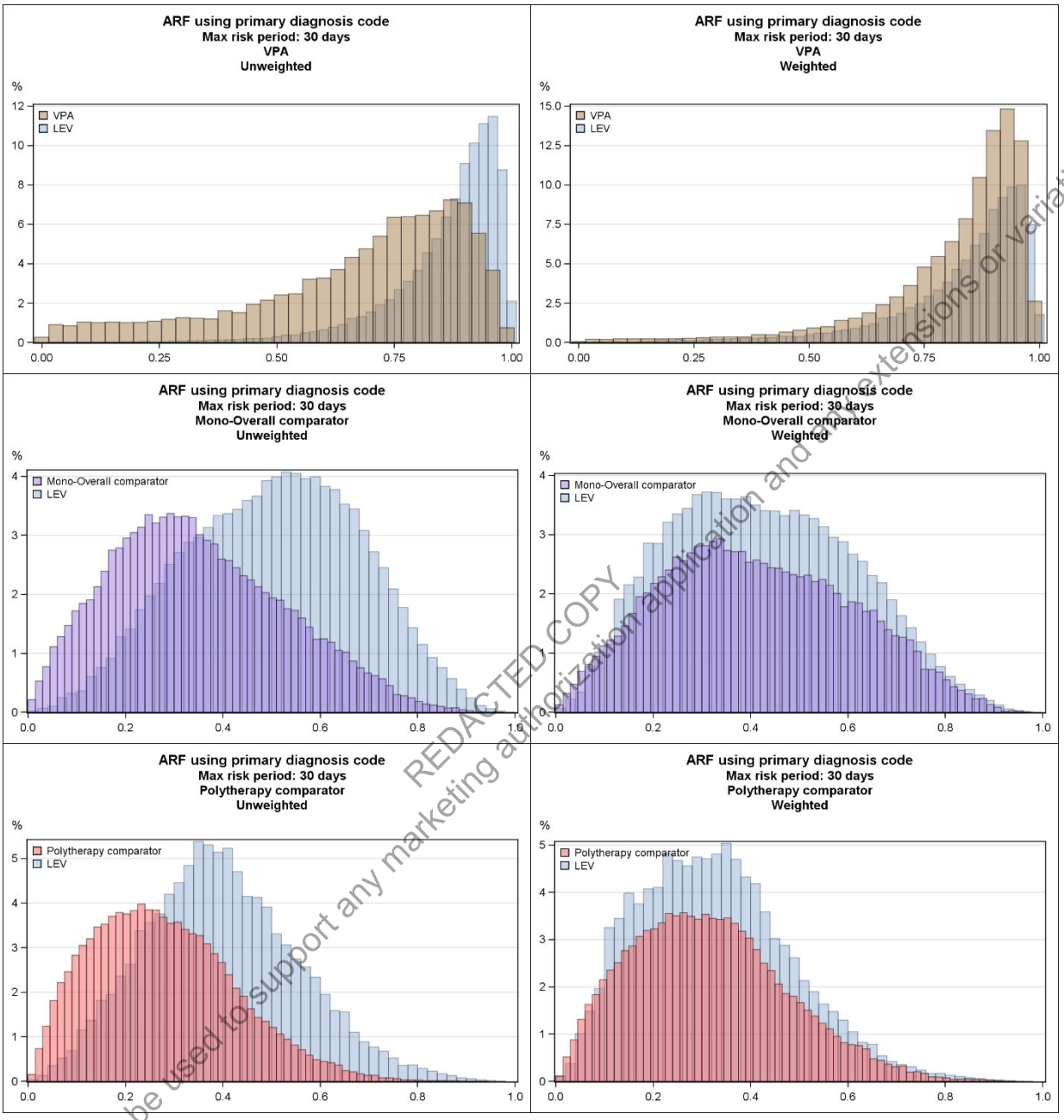

Figure 6 Unweighted and weighted PS distributions for levetiracetam (LEV) and valproic acid (VPA), "Monotherapy" all AEDs comparator and "polytherapy" analysis groups. Y-axis shows the percentage of participants, x-axis shows propensity score.

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10.4.1.2 Weight distributions

Distribution of truncated stabilized inverse probability treatment weight for primary analysis are shown below in Table 12. All models show a relatively good distribution with a mean around 1 and no extreme values. Both monotherapy with overall AED comparators and polytherapy analyses achieve the best performance compared to the 1:1 analyses.

Table 12. Weight distributions for primary diagnosis analyses

	30 days		60 days		90 days	
Cohort	**Mean (SD)**	**Min - Max**	**Mean (SD)**	**Min - Max**	**Mean (SD)**	**Min - Max**
Carbamazepine	0.98 (0.22)	0.20 - 2.09	0.98 (0.22)	0.20 - 2.11	0.98 (0.22)	0.20 - 2.09
Gabapentin	0.95 (0.53)	0.16 - 4.38	0.95 (0.52)	0.16 - 4.29	0.95 (0.53)	0.16 - 4.42
Lamotrigine	0.97 (0.36)	0.24 - 2.90	0.97 (0.36)	0.24 - 2.94	0.97 (0.36)	0.24 - 2.90
Oxcarbazepine	0.97 (0.30)	0.30 - 2.54	0.97 (0.30)	0.30 - 2.59	0.97 (0.30)	0.30 - 2.58
Phenytoin	0.96 (0.36)	0.20 - 2.93	0.96 (0.36)	0.19 - 2.93	0.96 (0.37)	0.19 - 2.92
Topiramate	0.96 (0.53)	0.19 - 4.30	0.96 (0.53)	0.19 - 4.33	0.96 (0.53)	0.19 - 4.25
Valproic acid	0.98 (0.38)	0.21 - 3.18	0.98 (0.38)	0.21 - 3.12	0.98 (0.37)	0.21 - 3.08
Mono-Overall	0.99 (0.44)	0.50 - 3.08	0.99 (0.44)	0.49 - 3.08	0.99 (0.44)	0.50 - 3.07
Polytherapy	0.99 (0.36)	0.44 - 2.74	0.99 (0.36)	0.44 - 2.74	0.99 (0.36)	0.44 - 2.74

SD=Standard deviation; Min=Minimum; Max=Maximum

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10.4.1.3 Absolute standardized differences of baseline covariates

Absolute standardized differences in means were calculated after weighting by truncated stabilized IPTW in order to assess the presence of any residual differences in baseline covariates. Standardized difference < 0.1 indicate negligible difference (satisfactory balance) between the comparison cohorts and the covariate is considered to have achieved balance.

Standardized differences are shown in the figures below, before and after weighting for the covariates which show the highest level of differences. Again, analyses for "Monotherapy" (comparing LEV with other AEDs as one group) and polytherapy were well balanced as opposed to most 1:1 comparisons. Only valproic acid (VPA) had all covariates with standardized differences below 0.1.

In the 1:1 comparisons, many covariates remained imbalanced after weighting. For instance, models for carbamazepine, gabapentin, oxcarbazepine, phenytoin and topiramate still did not achieve balance on age after weighting (absolute standardized difference respectively: 0.12; 0.30; 0.29; 0.37; 0.14). Models for carbamazepine, lamotrigine, oxcarbazepine, and topiramate showed relatively high level of differences in patients who had all cause hospitalizations during baseline (absolute standardized difference respectively: 0.15; 0.14; 0.15, and 0.14).

In the 1:1 comparisons, only the model comparing LEV with valproic acid achieve a satisfactory balance on covariates of interest (see Figure 7, Figure 8, Figure 9, Figure 10).

When the number of patients increased in the "Monotherapy-overall" and "Polytherapy" analyses, all baseline covariates of interest achieved balance (see Figure 10, Figure 11).

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Figure 7 Absolute standardized differences, primary analysis "Monotherapy" comparing levetiracetam (LEV) to carbamazepine (CBZ) and gabapentin (GBP). The 20 highest standardized differences after weighting are included here, specific for each drug. X-axis shows absolute standardized difference.

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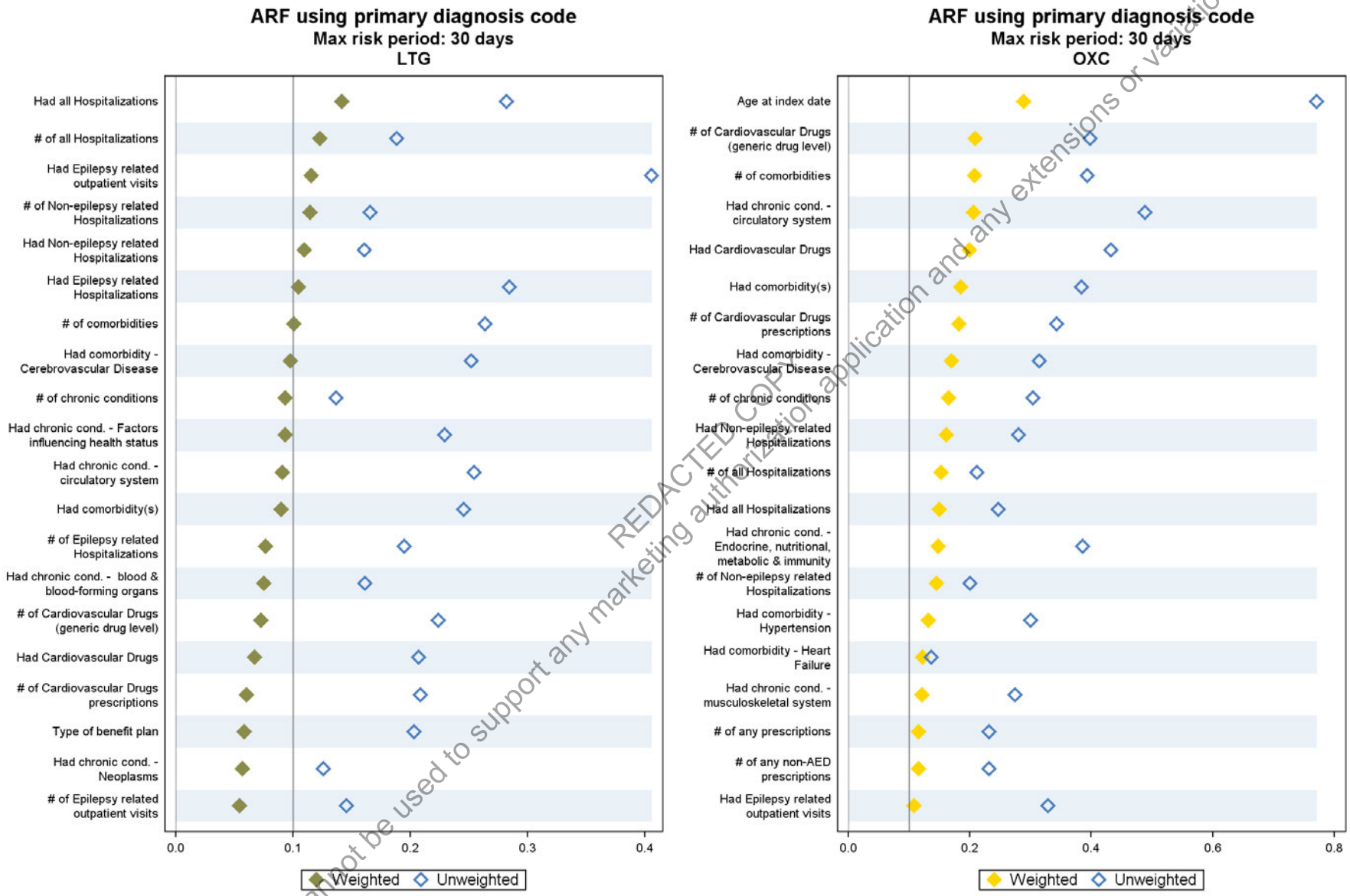

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Figure 8 Absolute standardized differences, primary analysis "Monotherapy" comparing levetiracetam (LEV) to lamotrigine (LTG), oxcarbazepine (OXC). The 20 highest standardized differences after weighting are included here, specific for each drug. X-axis shows absolute standardized difference.

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Figure 9 Absolute standardized differences, primary analysis "Monotherapy" comparing levetiracetam (LEV) to phenytoin (PHT) or topiramate (TPM). The 20 highest standardized differences after weighting are included here, specific for each drug. X-axis shows absolute standardized difference.

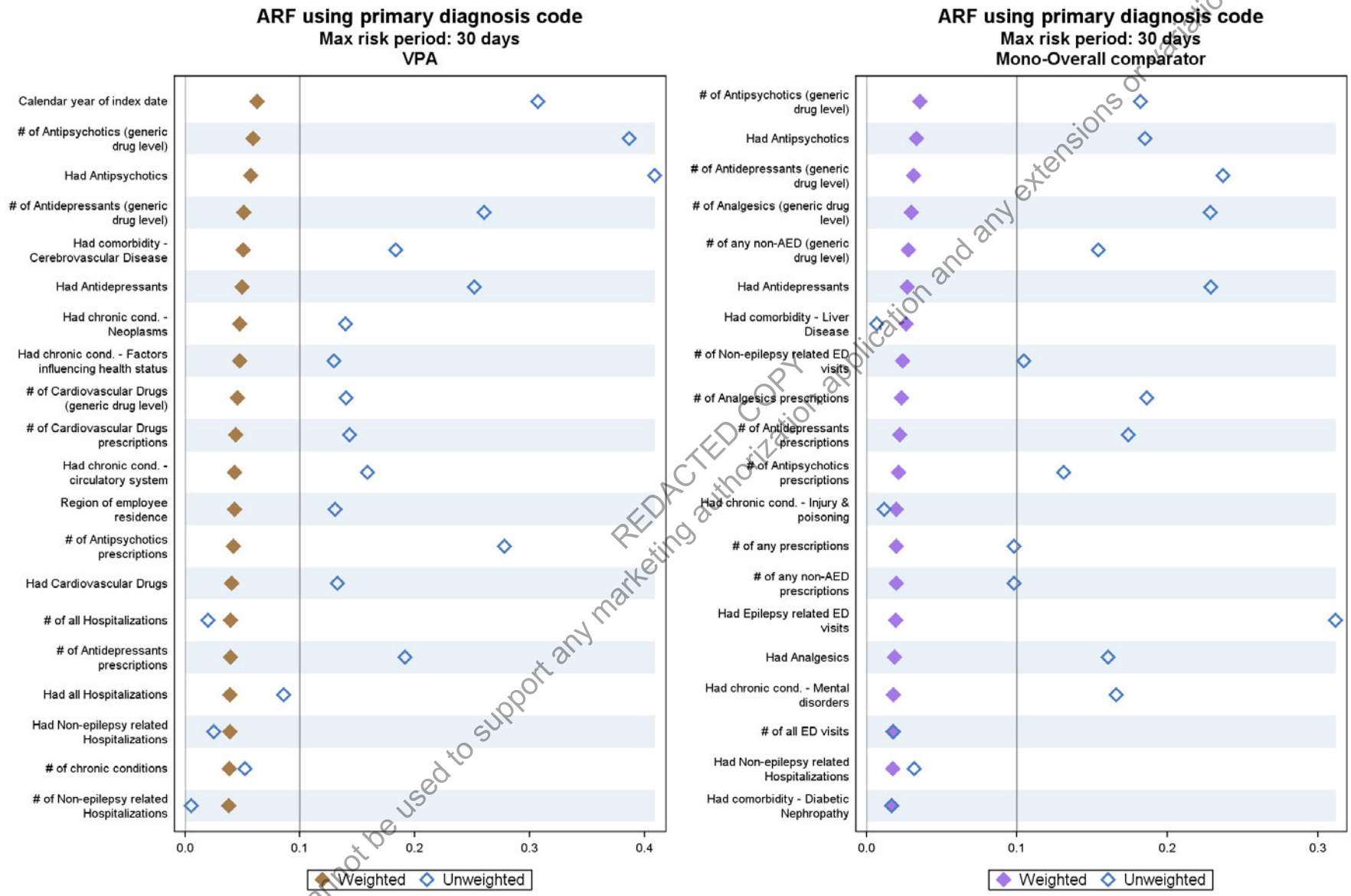

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Figure 10 Absolute standardized differences, primary analysis for analyses comparing levetiracetam to valproic acid (VPA) or the "Monotherapy"-all AEDs comparator group. The 20 highest standardized differences after weighting are included here. X-axis shows absolute standardized difference.

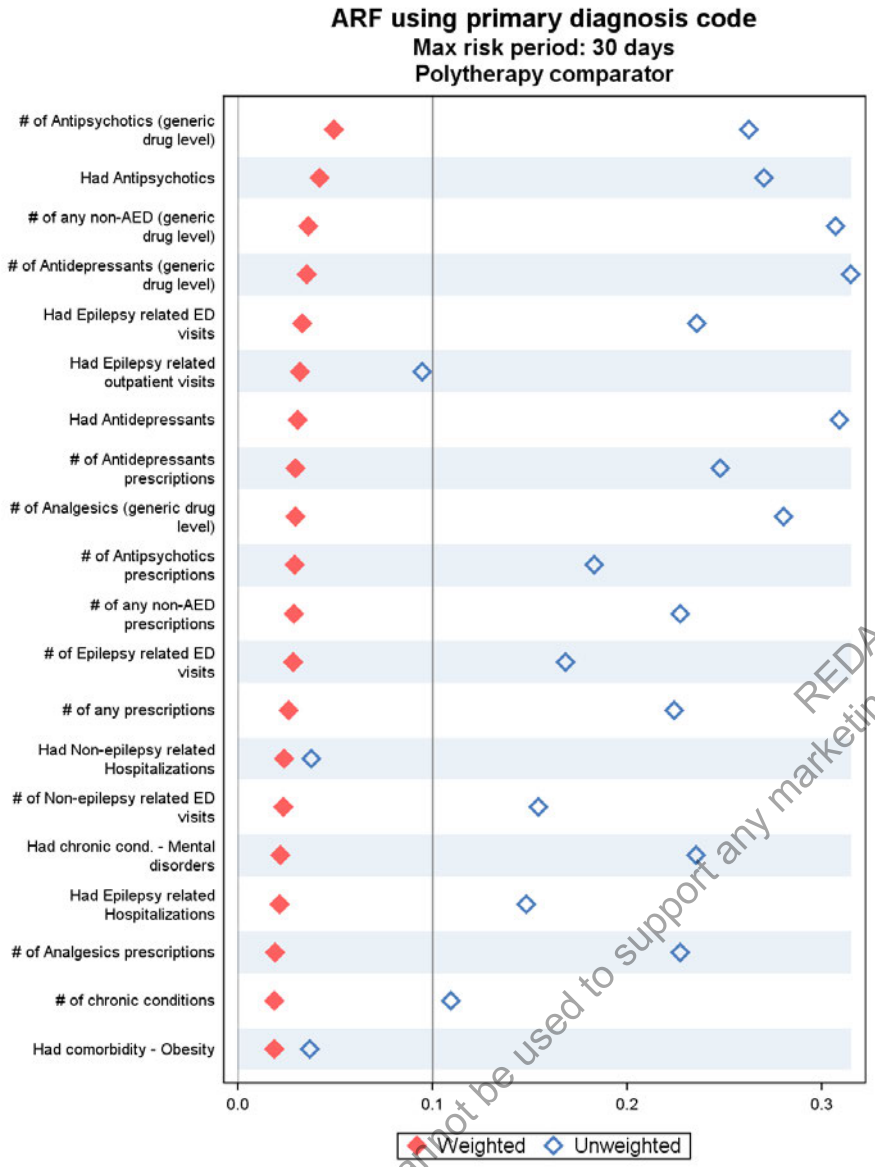

Figure 11 Absolute standardized differences, primary analysis "Polytherapy" comparing groups with and without levetiracetam. The 20 highest standardized differences after weighting are included here. X-axis shows absolute standardized difference

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10.4.1.4 Other model specifications for 1:1 analyses

Several different model specifications were performed to potentially improve balance of covariates. "Simple" logistic regression models were carried out using baseline comorbidities and co-medications (appendices 3 and 4 in the protocol) as binary variable, and as quintiles; include age as continuous, as quadratic, and age-groups. High dimensional propensity score model using confounder/exposure "risk ratio" as ranking method was also performed. However, these attempts did not provide any improvement in the balance of covariates for the 1:1 analyses.

Therefore, as commented previously, only the results of the valproic acid "Monotherapy analysis", the "Monotherapy" analysis comparing with the "all-AEDs Monotherapy" group, and the "Polytherapy" analysis show satisfying balance across all covariates of interest.

10.4.2 Results

Based on summary data provided by IBM® MarketScan® Research Databases, there was no missing data for age, gender and enrollment information. For the remaining demographic variables which include region (not provided for patients from Medicaid database) and health plan type the value "Unknown" was used for missing records and the results are showed in Table 7 and Table 11. Day supply values from all prescriptions were imputed as described in section 9.9.3.

10.4.2.1 Overall crude ARF rates in AED users

The crude incidence rate for ARF in epilepsy patients without known renal dysfunction taking AEDs is very low: Overall, in the "Monotherapy" cohort, a crude rate of ARF of **6.0 per 10,000 patients** was found (66 ARFs for 110,336 patients), and **6.5 per 10,000 patients** for the "Polytherapy" cohort (63 ARF for 96,215 patients) in the first 30 days after index date.

10.4.2.2 Incidence rate ratios for ARF in levetiracetam users vs. other AEDs used in monotherapy or polytherapy.

- Section A below presents results for the primary analysis. In 1:1 "Monotherapy" analyses, IRRs for ARFs in levetiracetam groups vs. other AEDs vary from 0.65 CI95% (0.16, 2.69) for carbamazepine to 12.88 CI95% (1.77, 93.77 for oxcarbazepine. However, as explained above, the balance of covariates was not achieved for most of these analyses due to the low number of patients in the comparator arms. When combining all AEDs together comparing LEV users to all other AED in **"Monotherapy",** the weighted IRR for ARF is **1.37 CI95% (0.80, 2.34)** decreasing to 1.26 CI95%(0.86-1.84) and 1.04 CI95% (0.76-1.44) respectively in the analyses 60 and 90 days after index date. For the analysis comparing LEV and other AEDs in **"Polytherapy", the IRR is 0.94 CI95% (0.51, 1.74)** decreasing

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to 0.77 CI95% (0.49-1.23) and increasing to 0.98 CI95% (0.68-1.42) in the analyses 60 and 90 days after index date.

- Section B presents sensitivity analyses using primary and secondary codes in order to identify ARF. In 1:1 comparisons, weighted IRRs vary from 0.61 CI95% (0.30, 1.24) for gabapentin to 3.49 CI95% (0.69, 17.56) for oxcarbazepine. However, as stated earlier, the balance of covariates was not achieved for most of these analyses due to the low number of patients in the comparator arms. When combining all AEDs together comparing LEV users to all other AED in "Monotherapy", the weighted IRR for ARF is 1.07 CI95% (0.75, 1.51) and 1.19 CI95% (0.82, 1.73) for the analysis comparing LEV and other AEDs in "Polytherapy" at 30 days after index date.

- When using a stricter definition of ARF using dialysis codes in section C, the numbers of ARFs are reduced further and therefore many analyses 1:1 in "Monotherapy" show comparator groups with zero ARFs. When comparing LEV and all other AEDs in "Monotherapy", the weighted IRR is 1.98 CI95% (0.43, 9.09) and 0.34 95% CI (0.07, 1.72) for the "Polytherapy" analysis comparing LEV Polytherapy users to all the other AED users in polytherapy at 30 days after index date.

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A. Incidence rate ratios (IRR) for ARF as primary diagnosis only in IBM® MarketScan® Databases, Monotherapy and Polytherapy analyses for 30 days (Primary analysis), 60 and 90 days after index date (sensitivity analyses)

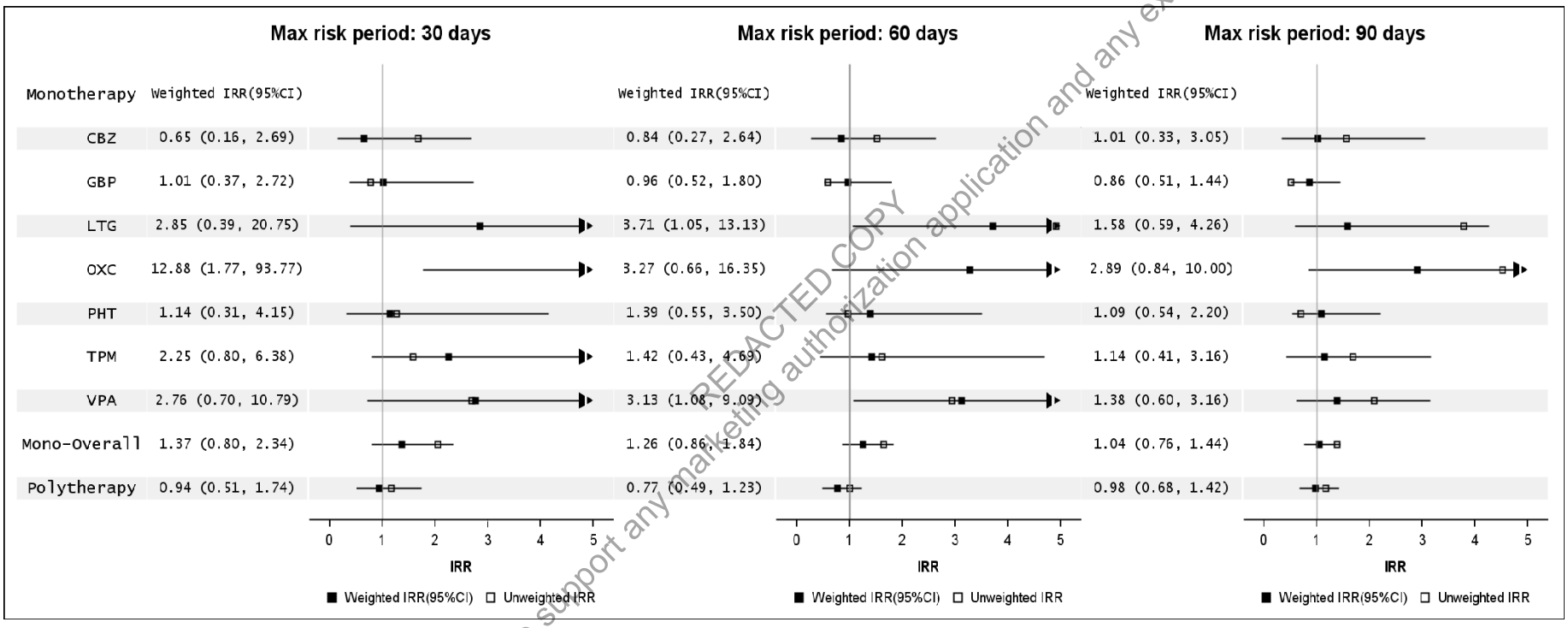

Figure 12 ARF as primary diagnosis only : Incidence Rate Ratios for levetiracetam vs. AED comparators (Monotherapy and polytherapy analysis) for 30 days (Primary analysis), 60 and 90 days after index date (sensitivity analyses) -weighted (solid square) and unweighted (empty squares) Baseline is the AED comparator group (not levetiracetam)

Max=Maximum;
IRR=Incidence rate ratio; CI=Confidence interval;
CBZ=Carbamazepine, GBP=Gabapentin, LTG=Lamotrigine, OXC=Oxcarbazepine, PHT=Phenytoin, TPM=Topiramate, VPA=Valproic acid

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Table 13 Table of IRRs for ARF comparing levetiracetam group to other AEDs (Monotherapy and Polytherapy) Maximum Risk window 30 days. Reference is the AED comparator (not levetiracetam)

		Levetiracetam				Comparator				
Model	Comparator	# patients	# ARF	person-months	IR (CI95%)	# patients	# ARF	person-months	IR (CI95%)	IRR (CI95%)
Unweighted	CBZ	45672,00	39	45180.93	8.63 (6.31, 11.81)	3914,00	2	3872.13	5.17 (1.29, 20.65)	1.67 (0.4, 6.92)
Weighted	CBZ	45604,53	38.36	45113.74	8.5 (6.2, 11.65)	2998,25	3.9	2965.56	13.15 (3.28, 52.76)	0.65 (0.16, 2.69)
Unweighted	GBP	45672,00	39	45180.93	8.63 (6.31, 11.81)	8208,00	9	8123	11.08 (5.76, 21.3)	0.78 (0.38, 1.61)
Weighted	GBP	45251,91	44.88	44741.72	10.03 (7.03, 14.31)	5808,10	5.7	5736.16	9.94 (3.93, 25.12)	1.01 (0.37, 2.72)
Unweighted	LTG	45672,00	39	45180.93	8.63 (6.31, 11.81)	9478,00	1	9385.57	1.07 (0.15, 7.56)	8.1 (1.11, 58.97)
Weighted	LTG	45526,97	34.86	45032.9	7.74 (5.65, 10.61)	8163,27	2.2	8083.46	2.72 (0.38, 19.28)	2.85 (0.39, 20.75)
Unweighted	OXC	45672,00	39	45180.93	8.63 (6.31, 11.81)	9005,00	1	8926.6	1.12 (0.16, 7.95)	7.71 (1.06, 56.09)
Weighted	OXC	45623,28	34.25	45147.24	7.59 (5.54, 10.39)	7487,23	0.44	7415.61	0.59 (0.08, 4.18)	12.88 (1.77, 93.77)
Unweighted	PHT	45672,00	39	45180.93	8.63 (6.31, 11.81)	7425,00	5	7330.13	6.82 (2.84, 16.39)	1.27 (0.5, 3.21)
Weighted	PHT	45484,59	46.45	44984.36	10.33 (7.41, 14.38)	5489,00	4.91	5417.9	9.06 (2.6, 31.57)	1.14 (0.31, 4.15)
Unweighted	TPM	45672,00	39	45180.93	8.63 (6.31, 11.81)	9287,00	5	9190.97	5.44 (2.26, 13.07)	1.59 (0.63, 4.03)
Weighted	TPM	45185,50	34.73	44683.83	7.77 (5.67, 10.66)	7828,11	2.68	7771.42	3.45 (1.28, 9.29)	2.25 (0.8, 6.38)
Unweighted	VPA	45672,00	39	45180.93	8.63 (6.31, 11.81)	9442,00	3	9356.9	3.21 (1.03, 9.94)	2.69 (0.83, 8.71)
Weighted	VPA	45316,90	36.93	44829.5	8.24 (5.99, 11.33)	8622,64	2.55	8550.85	2.99 (0.79, 11.26)	2.76 (0.7, 10.79)
Unweighted	**Monotherapy-overall**	**45672,00**	**39**	**45180.93**	**8.63 (6.31, 11.81)**	**64664,00**	**27**	**64006.13**	**4.22 (2.89, 6.15)**	**2.05 (1.25, 3.34)**
Weighted	**Monotherapy-Overall**	**44446,04**	**32.52**	**43951.31**	**7.4 (5.31, 10.31)**	**64483,81**	**34.48**	**63830.62**	**5.4 (3.55, 8.22)**	**1.37 (0.8, 2.34)**
Unweighted	**Polytherapy**	**30426,00**	**22**	**30102.63**	**7.31 (4.81, 11.1)**	**65789,00**	**41**	**65117.1**	**6.3 (4.64, 8.55)**	**1.16 (0.69, 1.95)**
Weighted	**Polytherapy**	**29359,82**	**19.17**	**29041.08**	**6.6 (3.93, 11.09)**	**65679,56**	**45.64**	**65014.37**	**7.02 (5.06, 9.73)**	**0.94 (0.51, 1.74)**

ARF=Acute renal failure;
IR=Incidence rate; IRR=Incidence rate ratio; CI=Confidence interval;
CBZ=Carbamazepine, GBP=Gabapentin, LTG=Lamotrigine, OXC=Oxcarbazepine, PHT=Phenytoin, TPM=Topiramate, VPA=Valproic acid

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Additional Table 19 and Table 20 for 60 and 90 days risk windows can be found in appendix 2.

B. Incidence rate ratios (IRR) for ARF using primary and secondary ARF codes in IBM® MarketScan® Databases Monotherapy and Polytherapy analyses for 30 days (Primary analysis), 60 and 90 days after index date (sensitivity analyses)

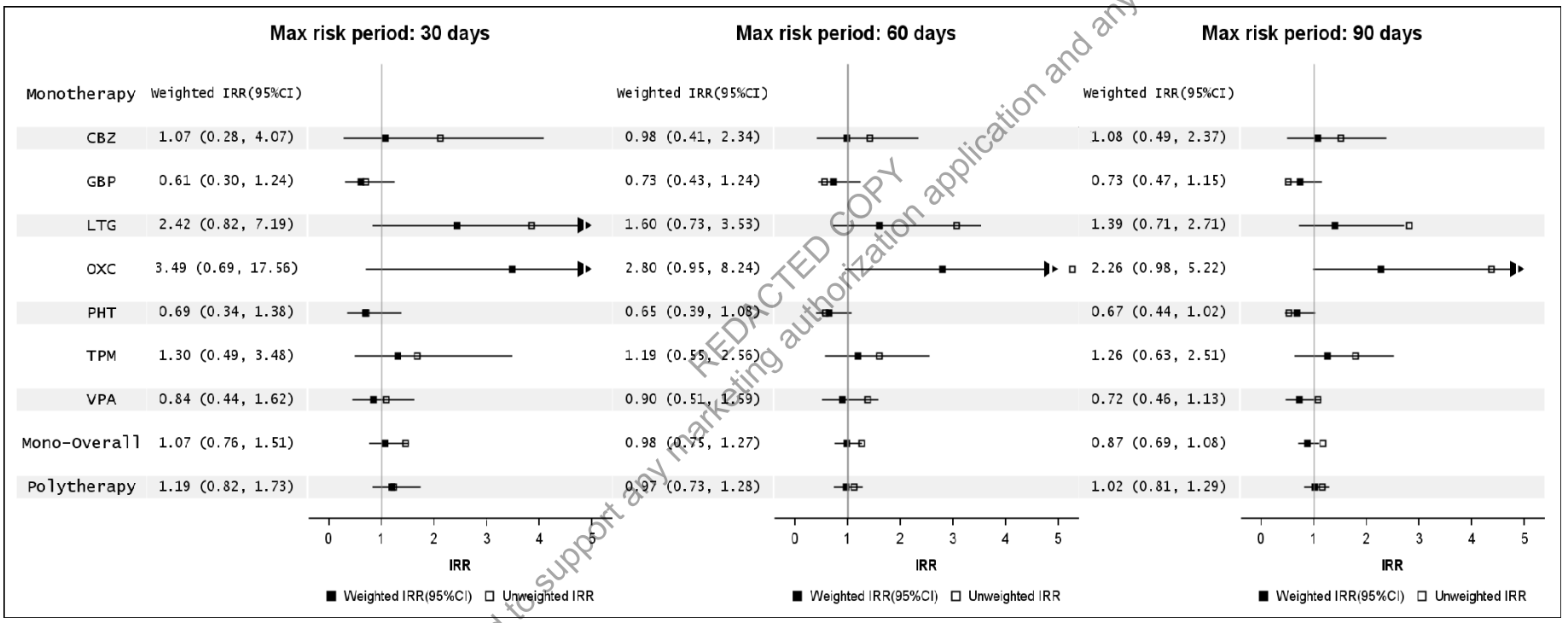

Figure 13 ARF using primary and secondary ARF codes in IBM® MarketScan® Databases: Incidence Rate Ratios for levetiracetam vs. AED comparators (Monotherapy and polytherapy analysis) for 30 days (Primary analysis), 60 and 90 days after index date (sensitivity analyses) -weighted (solid square) and unweighted (empty squares)

Max=Maximum;
IRR=Incidence rate ratio; CI=Confidence interval;
CBZ=Carbamazepine, GBP=Gabapentin, LTG=Lamotrigine, OXC=Oxcarbazepine, PHT=Phenytoin, TPM=Topiramate, VPA=Valproic acid

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Table 14 Table of IRRs for ARF (Primary and secondary codes in IBM® MarketScan® Databases) comparing levetiracetam group to other AEDs (Monotherapy and Polytherapy) Maximum Risk window 30 days. Reference is the AED comparator (not levetiracetam)

		Levetiracetam				Comparator				
Model	Comparator	# patients	# ARF	person -months	IR (CI95%)	# patients	# ARF	person -months	IR (CI95%)	IRR (CI95%)
Unweighted	CBZ	45672,00	74	45159.47	16.39 (13.05, 20.58)	3914,00	3	3871.1	7.75 (2.5, 24.03)	2.11 (0.67, 6.71)
Weighted	CBZ	45605,22	72.15	45093.45	16 (12.73, 20.11)	2989,75	4.41	2956.38	14.93 (4, 55.65)	1.07 (0.28, 4.07)
Unweighted	GBP	45672,00	74	45159.47	16.39 (13.05, 20.58)	8208,00	19	8116.97	23.41 (14.93, 36.7)	0.7 (0.42, 1.16)
Weighted	GBP	45223,14	83.55	44688.34	18.7 (14.53, 24.06)	5836,37	17.61	5756.88	30.59 (15.82, 59.18)	0.61 (0.3, 1.24)
Unweighted	LTG	45672,00	74	45159.47	16.39 (13.05, 20.58)	9478,00	4	9384.6	4.26 (1.6, 11.36)	3.84 (1.41, 10.51)
Weighted	LTG	45534,13	66.06	45021.84	14.67 (11.67, 18.44)	8162,07	4.89	8079.52	6.05 (2.09, 17.5)	2.42 (0.82, 7.19)
Unweighted	OXC	45672,00	74	45159.47	16.39 (13.05, 20.58)	9005,00	2	8926.5	2.24 (0.56, 8.96)	7.31 (1.8, 29.79)
Weighted	OXC	45626,03	64.63	45131.08	14.32 (11.4, 17.99)	7494,24	3.05	7421.76	4.11 (0.83, 20.35)	3.49 (0.69, 17.56)
Unweighted	PHT	45672,00	74	45159.47	16.39 (13.05, 20.58)	7425,00	17	7322.93	23.21 (14.43, 37.35)	0.71 (0.42, 1.2)
Weighted	PHT	45484,68	84.63	44961	18.82 (14.82, 23.91)	5479,85	14.75	5402.32	27.3 (14.19, 52.53)	0.69 (0.34, 1.38)
Unweighted	TPM	45672,00	74	45159.47	16.39 (13.05, 20.58)	9287,00	9	9188.43	9.79 (5.1, 18.82)	1.67 (0.84, 3.34)
Weighted	TPM	45199,98	66.84	44677.35	14.96 (11.86, 18.88)	7807,81	8.92	7747.84	11.52 (4.43, 29.97)	1.3 (0.49, 3.48)
Unweighted	VPA	45672,00	74	45159.47	16.39 (13.05, 20.58)	9442,00	14	9349.1	14.97 (8.87, 25.29)	1.09 (0.62, 1.94)
Weighted	VPA	45307,76	70.25	44800.39	15.68 (12.43, 19.78)	8603,76	15.85	8521.59	18.6 (10.09, 34.29)	0.84 (0.44, 1.62)
Unweighted	**Monotherapy-overall**	**45672,00**	**74**	**45159.47**	**16.39 (13.05, 20.58)**	**64664,00**	**72**	**63978.43**	**11.25 (8.93, 14.18)**	**1.46 (1.05, 2.01)**
Weighted	**Monotherapy-Overall**	**44454,96**	**60.92**	**43941.47**	**13.86 (10.89, 17.65)**	**64478,91**	**82.7**	**63796.8**	**12.96 (10.11, 16.63)**	**1.07 (0.76, 1.51)**
Unweighted	**Polytherapy**	**30426,00**	**57**	**30087**	**18.95 (14.61, 24.56)**	**65789,00**	**100**	**65087.23**	**15.36 (12.63, 18.69)**	**1.23 (0.89, 1.71)**
Weighted	**Polytherapy**	**29356,80**	**54.54**	**29021.02**	**18.79 (13.76, 25.67)**	**65683,44**	**102.45**	**64990.03**	**15.76 (12.83, 19.37)**	**1.19 (0.82, 1.73)**

ARF=Acute renal failure;
IR=Incidence rate; IRR=Incidence rate ratio; CI=Confidence interval;
CBZ=Carbamazepine, GBP=Gabapentin, LTG=Lamotrigine, OXC=Oxcarbazepine, PHT=Phenytoin, TPM=Topiramate, VPA=Valproic acid

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C. Incidence rate ratios (IRR) for ARF using a stricter definition for ARF (sensitivity analyses)

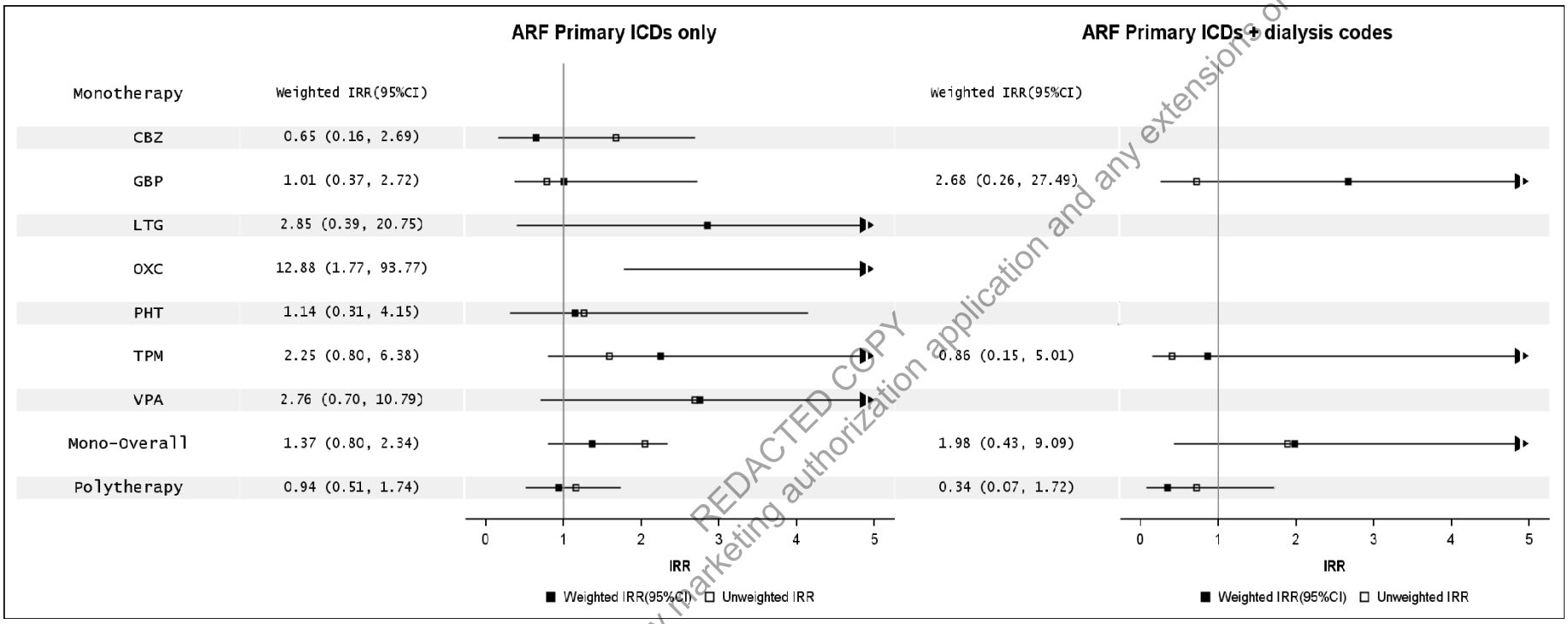

Figure 14 ARF primary code in IBM® MarketScan® Databases using a stricter definition with dialysis codes: Incidence Rate Ratios for levetiracetam vs. AED comparators (Monotherapy and polytherapy analysis) for 30 days (Primary analysis) only. -weighted (solid square) and unweighted (empty squares)

ICD=International Classification of Diseases;
IRR=Incidence rate ratio; CI=Confidence interval;
CBZ=Carbamazepine, GBP=Gabapentin, LTG=Lamotrigine, OXC=Oxcarbazepine, PHT=Phenytoin, TPM=Topiramate, VPA=Valproic acid

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D. Other sensitivity analyses

Three additional sensitivity analyses were carried out

- A minimum of 30 days continuous enrolment during follow-up period for all patients included in the analysis (Figure 17 *Incidence rate ratios for ARF : Sensitivity analysis with a minimum of 30 days enrolment for all patients included in the analysis Incidence Rate Ratios for levetiracetam vs. AED comparators (Monotherapy and polytherapy analysis) for 30 days (Primary analysis) only. -weighted (solid square) and unweighted (empty squares). Levetiracetam group as reference.*)
- Censoring patients at the date of prescription of another AED after index date (Figure 18 *Incidence rate ratios for ARF : Sensitivity analysis censoring patients at the date of prescription of another AED after index date. Incidence Rate Ratios for levetiracetam vs. AED comparators (Monotherapy and polytherapy analysis) for 30 days (Primary analysis) only. -weighted (solid square) and unweighted (empty squares). Levetiracetam group as reference.*)
- Study end date as 30th of Sep, 2015, date of the transition of the database from ICD-9-CM to ICD-10-CM (Figure 19 *Incidence rate ratios for ARF : Sensitivity analysis comparing the results of the study before and after October 2015, date of the transition of the database from ICD-9-CM to ICD-10-CM . Incidence Rate Ratios for levetiracetam vs. AED comparators (Monotherapy and polytherapy analysis) for 30 days (Primary analysis) only. -weighted (solid square) and unweighted (empty squares). Levetiracetam group as reference.*)

These sensitivity analyses are presented in Section 15.2 as they show no or very little difference with analyses presented in Figure 12.

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10.4.2.3 Absolute rate differences in ARF

Table 15 shows weighted incidence rates of ARF and absolute rate difference for the primary analysis (30 days risk window)

The graphs presented in Figure 15 and Figure 16 show the weighted incidence rates at 30, 60 and 90 days after index date for LEV vs. valproic acid, for the overall AED monotherapy comparison, and the polytherapy comparison which are the comparisons where a satisfying balance of covariates was achieved.

The absolute difference in the weighted rates of ARF at 30 days in the Monotherapy analysis comparing LEV users to all the other AEDs shows a potential difference of 2 additional ARFs per 10,000 patients months for LEV users although CI95% are showing substantial overlapping.

The valproic acid analysis shows a potential difference of 5 additional ARFs per 10,000 patient months for the LEV group, although the CI95% for this analysis show substantial overlapping due to the fact that there were only 3 ARFs in the valproic acid users group.

The polytherapy analysis shows very similar weighted rates of ARFs for the primary analysis (6.6 vs 7.02), i.e., a potential difference of 0.42 less ARF per 10,000 patient months for LEV users.

All differences between the groups are substantially reduced for analyses of the risk at 60 and 90 days.

Table 15 Weighted incidence rates of ARF and absolute rate difference for the primary analysis (30 days risk window)

	Levetiracetam			Comparator			
Cohort	**# ARF**	**person -months**	**IR (CI95%)**	**# ARF**	**person -months**	**IR (CI95%)**	**Abs Diff**
Carbamazepine	38.36	45113.74	8.5 (6.2, 11.65)	3.9	2965.56	13.15 (3.28, 52.76)	4.65
Gabapentin	44.88	44741.72	10.03 (7.03, 14.31)	5.7	5736.16	9.94 (3.93, 25.12)	0.09
Lamotrigine	34.86	45032.9	7.74 (5.65, 10.61)	2.2	8083.46	2.72 (0.38, 19.28)	5.03
Oxcarbazepine	34.25	45147.24	7.59 (5.54, 10.39)	0.44	7415.61	0.59 (0.08, 4.18)	7
Phenytoin	46.45	44984.36	10.33 (7.41, 14.38)	4.91	5417.9	9.06 (2.6, 31.57)	1.27
Topiramate	34.73	44683.83	7.77 (5.67, 10.66)	2.68	7771.42	3.45 (1.28, 9.29)	4.32
Valproic acid	36.93	44829.5	8.24 (5.99, 11.33)	2.55	8550.85	2.99 (0.79, 11.26)	5.25
Mono-Overall	**32.52**	**43951.31**	**7.4 (5.31, 10.31)**	**34.48**	**63830.62**	**5.4 (3.55, 8.22)**	**2**
Polytherapy	**19.17**	**29041.08**	**6.6 (3.93, 11.09)**	**45.64**	**65014.37**	**7.02 (5.06, 9.73)**	**0.42**

ARF=Acute renal failure; IR=Incidence rate; IRR=Incidence rate ratio; CI=Confidence interval

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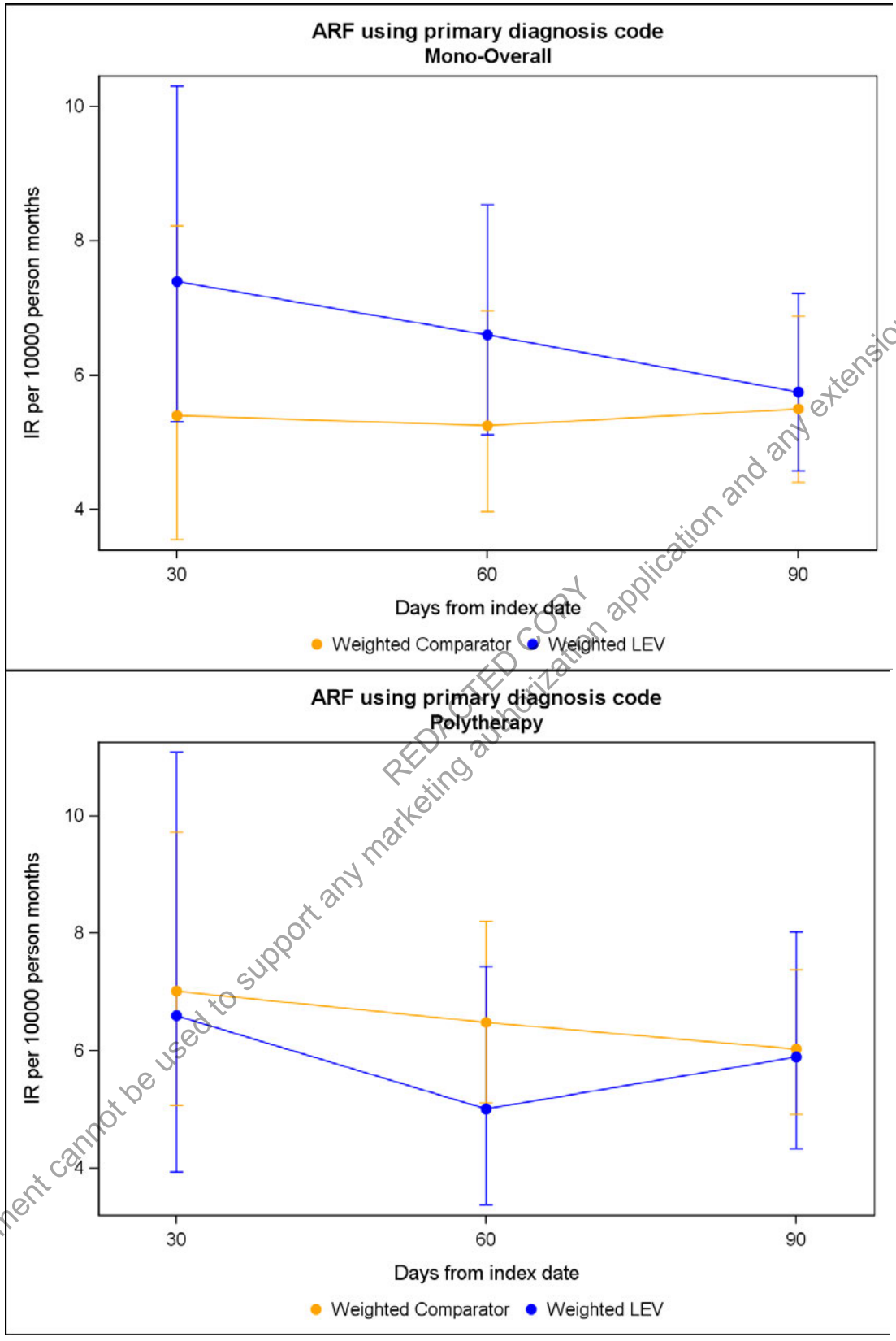

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Figure 15 Graphical representation of weighted Incidence Risk (IR per 10,000 patient-months) for the Monotherapy analysis (levetiracetam vs. all other AEDs) and the Polytherapy analysis (levetiracetam vs. other AEDs Polytherapy) at 30, 60 and 90 days.

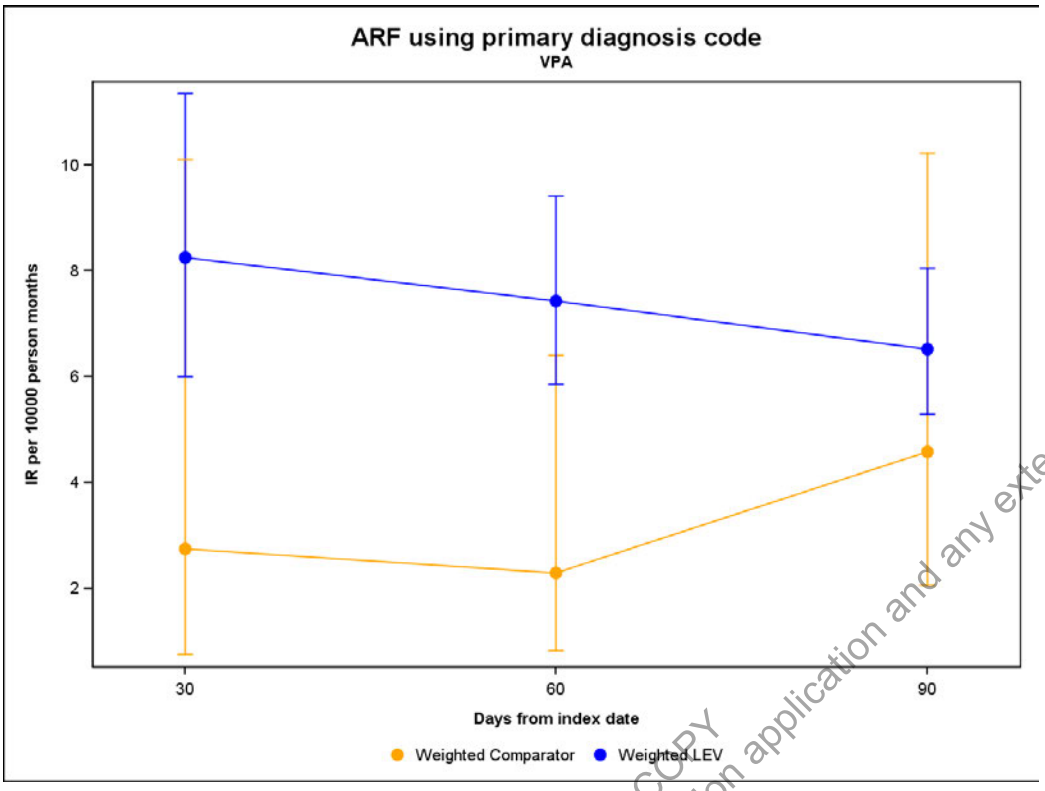

Figure 16 Graphical representation of weighted Incidence Risk (IR per 10,000 patient-months) for the Monotherapy analysis (levetiracetam vs. valproic acid)

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10.5 Other analyses (Stratified by age, gender and database type)

The Primary analysis was stratified by age groups, gender and type of database. All of these analyses did not achieve satisfactory balance of covariates except those presented in the Table 16, Table 17, and Table 18. In addition, many of these sub-analyses showed extremely low numbers in ARFs, resulting in wider CI95% with many groups with zero ARFs.

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Table 16 Primary analysis stratified by age-group. (only analyses showing balance of covariates are shown here)

				Levetiracetam				Comparator				
Analysis	Model	Age Group	Comparator	# patients	# ARF	person -months	IR (CI95%)	# patients	# ARF	person -months	IR (CI95%)	IRR (CI95%)
Polytherapy	Unweighted	46-64	All AEDs polytherapy	8012,00	15	7919.87	18.94 (11.42, 31.42)	18383,00	25	18183.7	13.75 (9.29, 20.35)	1.38 (0.73, 2.61)
	Weighted	46-64	All AEDs polytherapy	7794,68	14.83	7701.47	19.26 (10.22, 36.27)	18129,45	27.48	17931.53	15.32 (10.04, 23.37)	1.26 (0.59, 2.69)

ARF=Acute renal failure; IR=Incidence rate; IRR=Incidence rate ratio; CI=Confidence interval

Table 17 Primary analysis stratified by gender. (only analyses showing balance of covariates are shown here)

				Levetiracetam				Comparator				
Analysis	Model	Sex	Comparator	# patients	# ARF	person -months	IR (CI95%)	# patients	# ARF	person -months	IR (CI95%)	IRR (CI95%)
Monotherapy	Unweighted	Male	Valproic acid	22997,00	26	22751.97	11.43 (7.78, 16.78)	5774,00	2	5719.7	3.5 (0.87, 13.98)	3.27 (0.78, 13.77)
	Weighted	Male	Valproic acid	23552,89	25.3	23302.83	10.86 (7.34, 16.07)	4623,52	1.77	4583.41	3.87 (0.7, 21.27)	2.81 (0.49, 16.16)
	Unweighted	Male	Monotherapy-overall	22997,00	26	22751.97	11.43 (7.78, 16.78)	29936,00	15	29641.03	5.06 (3.05, 8.39)	2.26 (1.2, 4.26)
	Weighted	Male	Monotherapy-overall	21443,88	22.35	21213.58	10.53 (6.98, 15.89)	30993,26	18.71	30691.82	6.1 (3.48, 10.66)	1.73 (0.86, 3.46)
	Unweighted	Female	Monotherapy-overall	22675,00	13	22428.97	5.8 (3.37, 9.98)	34728,00	12	34365.1	3.49 (1.98, 6.15)	1.66 (0.76, 3.64)
	Weighted	Female	Monotherapy-overall	23002,16	10.17	22737.73	4.47 (2.57, 7.8)	33490,56	15.77	33138.8	4.76 (2.52, 8.97)	0.94 (0.4, 2.18)
Polytherapy	Unweighted	Male	All AEDs polytherapy	13805,00	12	13670.73	8.78 (4.99, 15.46)	26847,00	20	26591.33	7.52 (4.85, 11.66)	1.17 (0.57, 2.39)
	Weighted	Male	All AEDs polytherapy	12485,18	7.97	12368.95	6.45 (3.59, 11.59)	27761,96	25.32	27492.41	9.21 (5.77, 14.7)	0.7 (0.33, 1.48)
	Unweighted	Female	All AEDs polytherapy	16621,00	10	16431.9	6.09 (3.27, 11.31)	38942,00	21	38525.77	5.45 (3.55, 8.36)	1.12 (0.53, 2.37)
	Weighted	Female	All AEDs polytherapy	16874,64	11.2	16672.13	6.72 (3.07, 14.71)	37917,60	20.33	37521.96	5.42 (3.47, 8.46)	1.24 (0.5, 3.05)

ARF=Acute renal failure; IR=Incidence rate; IRR=Incidence rate ratio; CI=Confidence interval

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Table 18 Primary analysis, stratified by type of database (only analyses showing balance of covariates are shown here)

				Levetiracetam				Comparator				
Analysis	Model	Source	Comparator	# patients	# ARF	person -months	IR (CI95%)	# patients	# ARF	person -months	IR (CI95%)	IRR (CI95%)
Monotherapy	Unweighted	CCAE/MDCR	Valproic acid	29487,00	28	29129.57	9.61 (6.64, 13.92)	5548,00	2	5486.83	3.65 (0.91, 14.57)	2.64 (0.63, 11.07)
	Weighted	CCAE/MDCR	Valproic acid	28864,55	26.98	28514.86	9.46 (6.49, 13.8)	5444,94	1.77	5387.97	3.29 (0.6, 18.09)	2.88 (0.5, 16.5)
Polytherapy	Unweighted	CCAE/MDCR	All AEDs polytherapy	19572,00	11	19334.63	5.69 (3.15, 10.27)	38639,00	20	38180.17	5.24 (3.38, 8.12)	1.09 (0.52, 2.27)
	Weighted	CCAE/MDCR	All AEDs polytherapy	17946,91	7.39	17715.05	4.17 (2.18, 7.98)	39709,92	22.82	39247.13	5.81 (3.65, 9.27)	0.72 (0.32, 1.6)
	Unweighted	MDCD	All AEDs polytherapy	10854,00	11	10768	10.22 (5.66, 18.45)	27150,00	21	26936.93	7.8 (5.08, 11.96)	1.31 (0.63, 2.72)
	Weighted	MDCD	All AEDs polytherapy	11412,91	11.78	11326.03	10.4 (4.97, 21.79)	25969,64	22.83	25767.23	8.86 (5.61, 14)	1.17 (0.49, 2.8)

ARF=Acute renal failure; IR=Incidence rate; IRR=Incidence rate ratio; CI=Confidence interval
CCAE/MDCR= IBM MarketScan® Commercial Database / IBM MarketScan® Medicare Supplemental Database; MDCD= IBM MarketScan® Multi-State Medicaid Database

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11 DISCUSSION

11.1 Key results

- This study has a new AEDs users design comparing the risk of ARF in LEV to other AEDs users, using an optimal short risk window and state-of-the-art analytical pharmacoepidemiology methods (High Dimensional Propensity Score and Inverse Probability of Treatment weights) in order to address baseline confounding.
- The use of levetiracetam in IBM® MarketScan® Databases is 5 to 10 times higher than the use of other AEDs.
- The overall crude rate of Acute Renal Failures following the use of a new AED in our study is very low for patients using AEDs in "Monotherapy" or in "Polytherapy" (**6.0 ARF per 10,000 patients** and **6.5 per 10,000 patients respectively** in the first 30 days after index date).
- Most analyses attempting to compare the risk of ARF in LEV users compared to other AEDs in 1:1 comparisons presented substantial imbalances in key covariates (e.g. age or baseline hospitalizations) after weighting despite several attempts to re-specify the models (see violation of positivity assumption in section 11.2.3). Therefore, interpreting these analyses with remaining confounding is not possible.
- To account for this issue, we produced an ad-hoc analysis comparing LEV new users to all other AED "Monotherapy" new users that achieved a better balance of key covariates that showed a weighted IRR of 1.37 CI95% (0.80, 2.34)) at 30 days after index date.
- This potential increase in cases represents 2 additional ARFs per 10,000 person-months for LEV users compared to other AED users in "Monotherapy" at 30 days as the risk of ARF in AED users is already very low
- In the "Polytherapy" analysis comparing the use of LEV to the use of other AEDs in polytherapy in the first 30 days of use, the weighted IRR was 0.94 CI95% (0.51, 1.74)).
- When using primary and secondary ARFs codes in the ARF outcome definition, the weighted IRR was 1.07 CI95% (0.75, 1.51) for LEV compared to all other AEDs for "Monotherapy" and a weighted IRR of 1.19 CI95% (0.82, 1.73) was found for "Polytherapy" at 30 days after index date.
- The results of the study were very robust to the sensitivity analyses performed.

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11.2 Limitations

Biases due to the study design and the nature of IBM® MarketScan® Research Databases are discussed in Section 9.6 of this document.

11.2.1 Power of the study and planned sample size

Section 9.7 on study size presents the power and sample size evaluation made in the last version of the protocol using an early approximation of the ARF rates which were previously expected in the study(15). Overall, the study identified a much higher number of patients than the 3000 minimum patients required in our originally planned sample size (110,336 patients "Monotherapy" and 96,215 patients "Polytherapy"). However, once the analysis was carried out, the rate of ARF in the database found was 10 times lower than the one expected. This is due to the fact that not all the inclusion/exclusion criteria were applied in the feasibility calculations (only a diagnosis of epilepsy at baseline was requested) and that the risk window for ARF was reduced to 30 days (60 or 90 days) as opposed to the total duration of AED treatment evaluated during the feasibility assessment.

ARF attrition Table 14, Table 15, and Table 16 show a crude rate of 6 per 10,000 patients ARFs for the "Monotherapy" cohort and 6.5 per 10,000 patients in the "Polytherapy" cohort in the first 30 days after index date as opposed to the rate of 50 per 10,000 anticipated in the previous sample calculations. In the "Monotherapy" analysis, only 710 ARF cases were included after excluding patients without a diagnosis of epilepsy at baseline (as opposed to 8159 anticipated in the previous calculation), which were further reduced by 91% when applying all the inclusion-exclusion criteria of the analysis.

Using the current number of patients identified in the study, the power of a standard two-sided Pearson Chi-square test against equal proportions of ARF would have been 33.6% when assuming a risk ratio for LEV vs "Other AEDs" of 1.5 in "Monotherapy" and using a significance level of 5%. The power of the same test in " Polytherapy" setting would have been 39.5%. The required total sample size for 80% power of this test would have been 375,758 when assuming a 1:1 ratio of numbers of participants in the LEV and "Other AEDs" in the monotherapy setting. The required total sample size in the polytherapy setting would have been 251,690.

11.2.2 Primary or secondary codes in IBM® MarketScan® Databases

Another explanation for the low rates of ARFs found in the primary analysis is that only primary diagnosis codes were included from emergency department or hospitalization. Diagnosis codes were classified as "primary" based on Watson Health admission construction methodology in IBM® MarketScan® Databases. Therefore, it is not possible to verify whether these primary diagnosis codes were clinically considered as "primary" by the treating clinicians. Moreover, other studies assessing the risk of ARF following the use of other types of medications chose to use codes in any position on the inpatient billing claim(24). Using the latter definition of ARF identification almost tripled the number of ARFs in the analysis, from 66 to 146 for the "Monotherapy" cohort and from 63 to 157 in the "Polytherapy" cohort. Analysis section B presents the results of the sensitivity analysis comparing the risk of ARFs in LEV vs. other AEDs patients for "Monotherapy" and "Polytherapy" using any codes of ARF in IBM®

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MarketScan® Databases showing a weighted IRR of 1.07 CI95% (0.75, 1.51) % LEV users compared to other AEDs for "Monotherapy" and a weighted IRR of 1.19 CI95% (0.82, 1.73) in ARF in LEV users compared to other AEDs for "Polytherapy".

11.2.3 Issues with the 1:1 comparisons between levetiracetam and other AEDs in Monotherapy.

One important observation made in this study is the difference in prescription volumes between LEV and all the other AEDs in IBM® MarketScan® Databases which had been previously observed in other studies (25). Levetiracetam is by far the most prescribed AED in the database, showing 5 to 10 times more patients with LEV prescriptions compared to patients with other AEDs prescriptions in monotherapy as shown Figure 2 making LEV the drug of choice in the treatment of epilepsy in the US. This important fact is likely to have a high impact on the type of patients using other AEDs as opposed to patients using other AEDs driven by specific characteristics of these medications. When comparing LEV users to other AEDs in 1:1 comparisons, the (unweighted) propensity score distributions illustrate very well how different these populations are at start in Figure 4, Figure 5, and Figure 6. Due to these substantial differences in the original patients' characteristics, most of the 1:1 comparison in "Monotherapy" did not achieve sufficient balance in the most relevant covariates after weighting despite using state-of-the-art methods and several attempts to address model misspecifications.

Positivity assumption violation: To be able to achieve adequate balance in baseline covariates, the exposure must be present at all the levels of the confounders (positivity assumption). This was violated in all those comparisons with small sample sizes and a high number of confounders and is the reason why balance for measured baseline variables was not achieved except in the largest comparisons.

For instance, in the analysis comparing levetiracetam to oxcarbazepine in "Monotherapy", the original descriptive data in Table 7 show that the average age of patients using levetiracetam is 30.3 years old compared to 14.0 years old for oxcarbazepine. In the oxcarbazepine group "Monotherapy", 81% of patients were under 18 years old compared to 44% in the LEV group. This is because oxcarbazepine is an AED of choice in children with focal seizures (26, 27). One solution would be to explore the analyses in adults and children separately as analyses stratified by age were produced. However, these analyses would reduce the number of patients substantially and would not allow us to achieve better balance in covariates (1:1 analyses "Monotherapy").

Interpreting the results of the comparisons of LEV "Monotherapy" users to other AEDs 1:1 is therefore very difficult.

The comparison with valproic acid in "Monotherapy" is the only comparison to achieve a satisfactory balance in covariates after weighting. Valproic acid is prescribed at only 20% of the volume of LEV in the current study (9,442 vs. 45,672 patients) and although the PS distributions in Figure 6 showed good overlapping after weighting, only 3 ARFs were present in patients using valproic acid in "Monotherapy". This number is too low to be able to conclude on the comparison with valproic acid and showing a 2.76 times higher increase in the incidence rate of ARF compared to LEV with a very wide 95% confidence interval crossing 1 (IRR of 2,76 CI95% (0.70, 10.79)). The low rate of ARFs found in the valproic acid group (2.99 per 10,000 patients CI95% (0.79, 11.26) could also be due to the fact that valproic acid has been previously highlighted in the literature for attenuating proteinuria and kidney injury due to its action as an inhibitor of histone deacetylase (HDAC)(28).

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11.2.4 Post-hoc analysis "Monotherapy" levetiracetam vs. all other AEDs

Due to the issue in interpreting the 1:1 "Monotherapy" analyses described above; we decided to include an additional analysis post hoc comparing the risk of ARF in LEV vs. all other AEDs in "Monotherapy". This analysis increased substantially the number of patients in the comparator group to 64,664 patients, and the model achieved a satisfactory balance of covariates. Nonetheless, as explained in section 11.2.1, due to the low rate of ARF, this analysis also could not achieve sufficient power to detect an IRR of 1.5.

11.2.5 Multiplicity of analyses

This study includes a very high number of analyses (12 "Monotherapy" 1:1 analyses, 1 additional "Monotherapy" analysis versus all other AEDs, 1, "Polytherapy analysis" and further 5 sensitivity analyses with additional stratified analyses for age, gender and type of database). Despite the high number of analyses performed in this study, due to the number of analyses that were not interpretable as they showed imbalance in covariates, our team chose not to apply the Bonferroni adjustment which would have only further increased the confidence intervals accounting for the multiplicity of analyses, but not affecting the estimates.

11.2.6 Interpretation

To our knowledge, this is the first study to analyze the risk of ARF in AED users in monotherapy or polytherapy.

One other study was found investigating the risk of acute renal injury in patients using AEDs. This study was carried out in Canada (Ontario) using a different design (LEV vs. non-use) and study endpoint (acute kidney injury, AKI). The measure of relative risk also showed a non-significant increase in the occurrence of AKI in LEV users compared to non-users in line with the current study (Odds Ratio 1.24; 95% confidence interval, 0.62 to 2.47) despite different choices in their patients selection(29). This study, using less restrictive exclusion criteria (only epilepsy diagnosis at baseline, evidence of end stage kidney disease and hospital discharge in the two days prior to index date) showed a rate of AKI of 30 per 10,000 patient-months **in adult** users at 30 days after LEV use. The analysis did not distinguish between monotherapy or polytherapy use. This difference in the crude rates of ARF occurrence in LEV patients of this study could be due to the less restrictive exclusion criteria of the Canadian study, the restriction to primary codes in the IBM® MarketScan® Databases, the pediatric population included in this study, and that AKI is a broader and more frequent study endpoint than ARF.

The EU-SmPC of Keppra (dated 3rd February 2020) includes wording in Section 4.4 (Special Warnings and Precautions) describing Acute kidney injury (see below) as well as referencing Acute kidney injury as a "rare side effect" (may affect 1 in 10,000 people) in section 4.8 (undesirable effects).

EU-SmPC Section 4.4"Acute Kidney injury
The use of levetiracetam has been very rarely associated with acute kidney injury, with a time to onset ranging from a few days to several months."

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The results of this study align with the SmPC.

11.3 Generalizability

The findings apply to patient populations with similar access to health care systems and similar AED utilization, and health care use patterns.

12 OTHER INFORMATION

N/A

13 CONCLUSION

The objective of the study was to compare the incidence rate of ARF among patients exposed to LEV versus other AEDs (as monotherapy or polytherapy) to further characterize the risk of renal failure in patients treated with AEDs.

The rate of ARFs in AED new users was found to be very low. The study showed a weighted IRR of 1.37 CI95% (0.8, 2.34)) in ARF risk for LEV users vs. other AEDs when used alone and a weighted IRR of 0.94 CI95% (0.51, 1.74) when used concomitantly with other AEDs. The IRR of 1.37 represents about 2 additional ARF cases per 10,000 patient months in "Monotherapy".

The risk of ARF in LEV users in this study is aligned with the current information included in the EU SmPC. The results of the study do not impact the current benefit-risk balance of the product.

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15 APPENDICES

15.1 APPENDIX 1. List of stand-alone documents

None

15.2 APPENDIX 2. Additional information

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Additional Sensitivity analyses

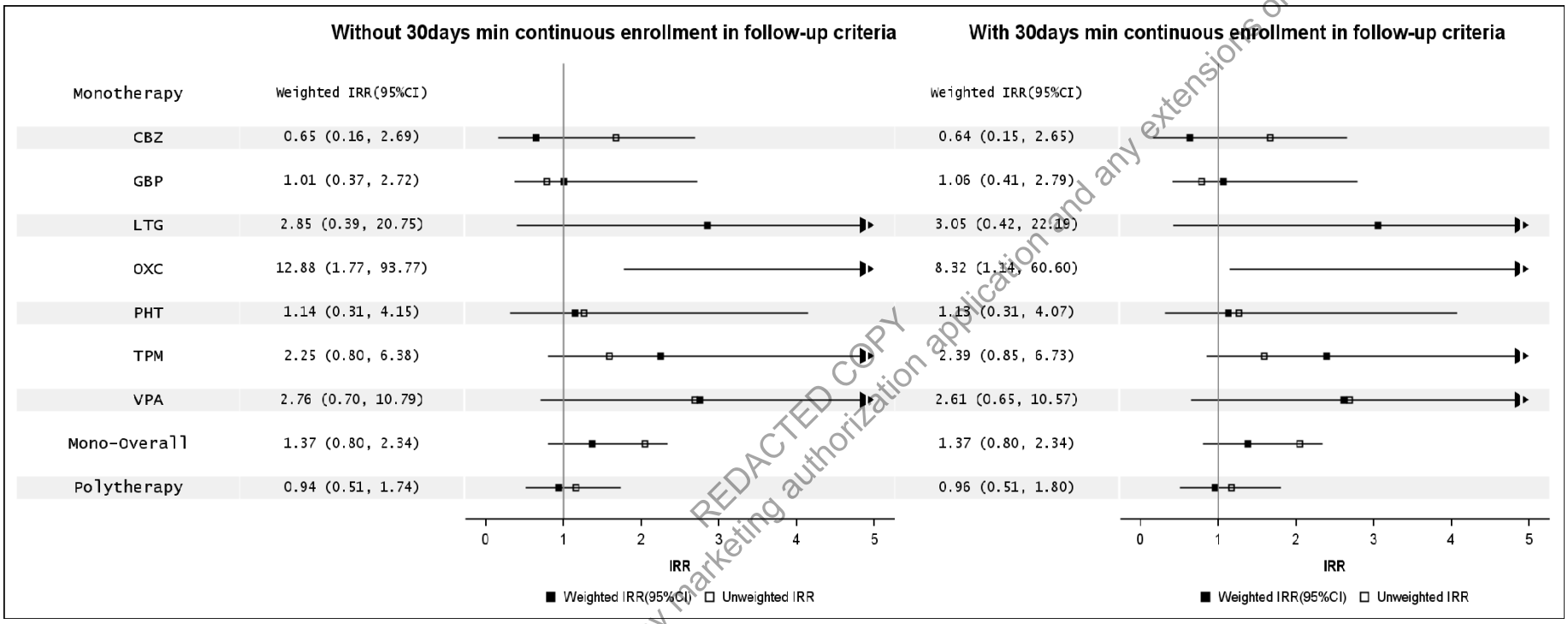

Figure 17 Incidence rate ratios for ARF : Sensitivity analysis with a minimum of 30 days enrolment for all patients included in the analysis Incidence Rate Ratios for levetiracetam vs. AED comparators (Monotherapy and polytherapy analysis) for 30 days (Primary analysis) only. -weighted (solid square) and unweighted (empty squares). Levetiracetam group as reference.

Min=Minimum;
IRR=Incidence rate ratio; CI=Confidence interval;
CBZ=Carbamazepine, GBP=Gabapentin, LTG=Lamotrigine, OXC=Oxcarbazepine, PHT=Phenytoin, TPM=Topiramate, VPA=Valproic acid

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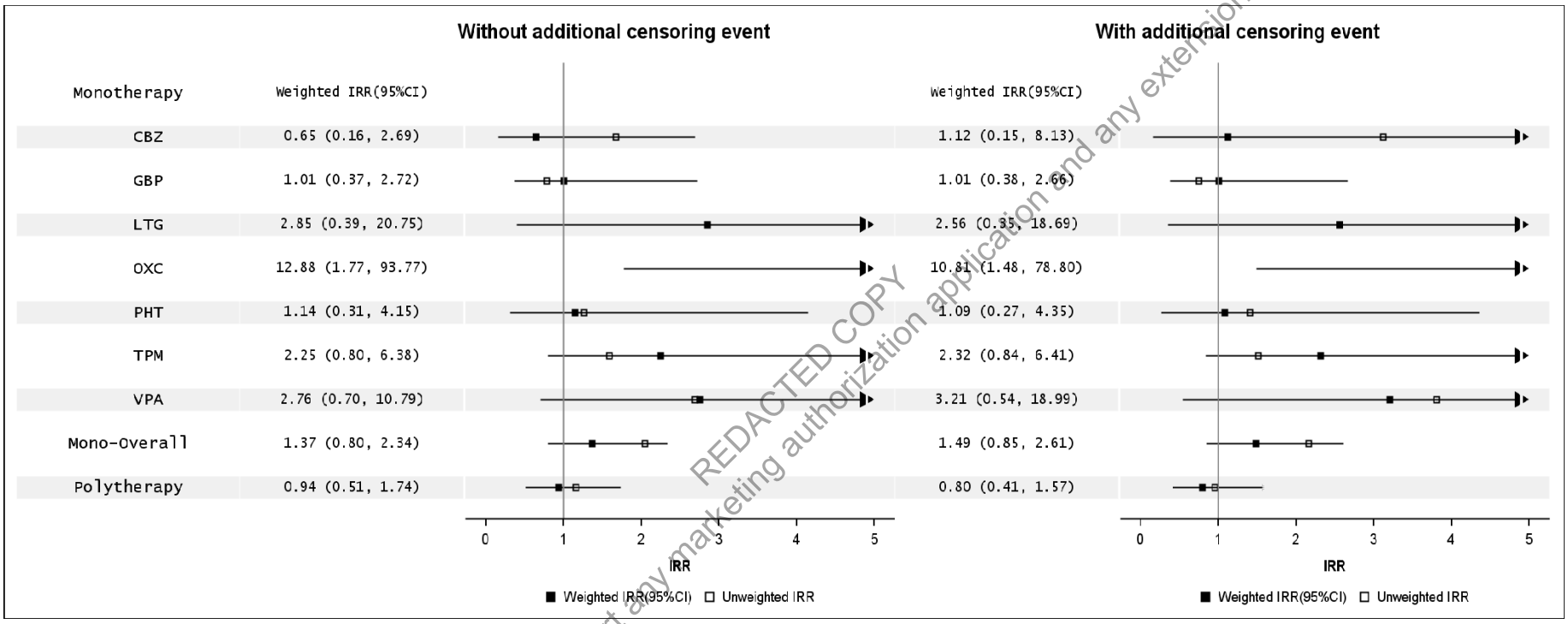

Figure 18 Incidence rate ratios for ARF : Sensitivity analysis censoring patients at the date of prescription of another AED after index date. Incidence Rate Ratios for levetiracetam vs. AED comparators (Monotherapy and polytherapy analysis) for 30 days (Primary analysis) only. -weighted (solid square) and unweighted (empty squares). Levetiracetam group as reference.

IRR=Incidence rate ratio; CI=Confidence interval;
CBZ=Carbamazepine, GBP=Gabapentin, LTG=Lamotrigine, OXC=Oxcarbazepine, PHT=Phenytoin, TPM=Topiramate, VPA=Valproic acid

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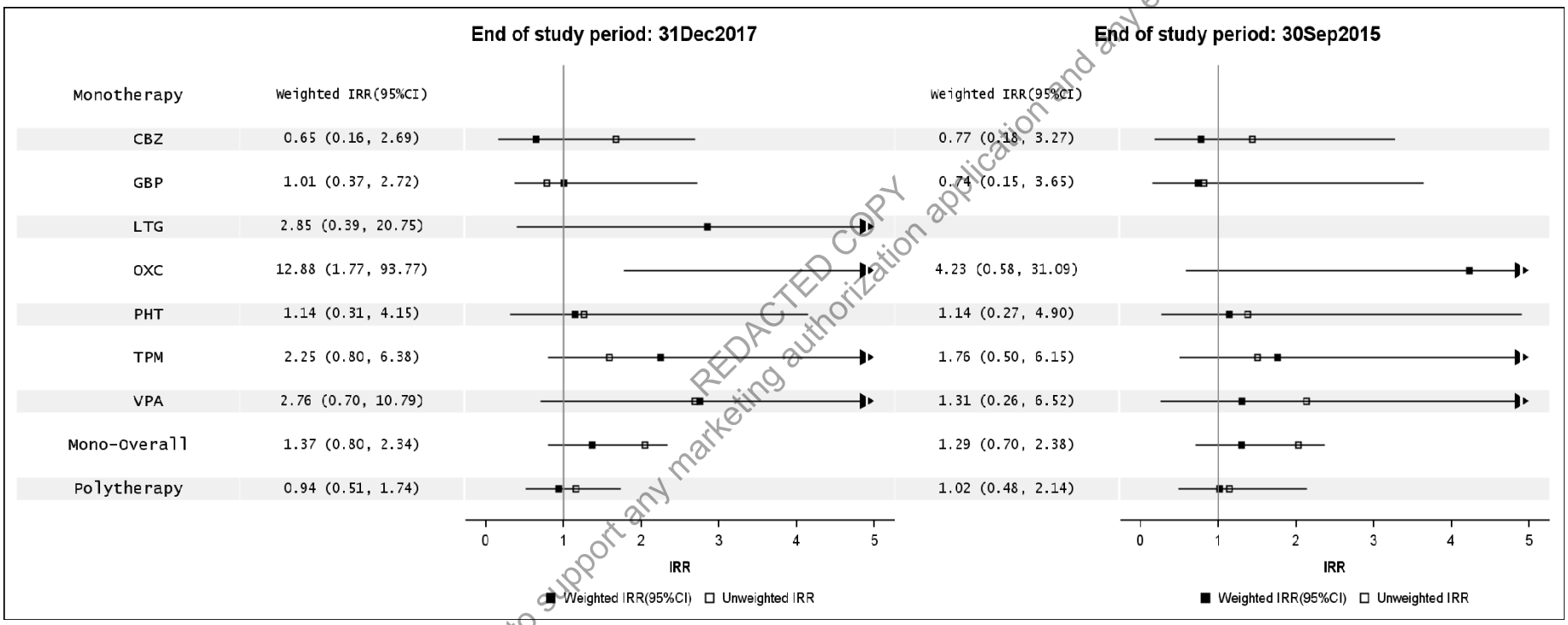

Figure 19 Incidence rate ratios for ARF : Sensitivity analysis comparing the results of the study before and after October 2015, date of the transition of the database from ICD-9-CM to ICD-10-CM . Incidence Rate Ratios for levetiracetam vs. AED comparators (Monotherapy and polytherapy analysis) for 30 days (Primary analysis) only. -weighted (solid square) and unweighted (empty squares). Levetiracetam group as reference.

IRR=Incidence rate ratio; CI=Confidence interval;
CBZ=Carbamazepine, GBP=Gabapentin, LTG=Lamotrigine, OXC=Oxcarbazepine, PHT=Phenytoin, TPM=Topiramate, VPA=Valproic acid

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Table 19 Table of IRRs for ARF comparing levetiracetam group to other AEDs (Monotherapy and Polytherapy) Maximum Risk window 60 days. Baseline is the AED comparator (not levetiracetam)

	Levetiracetam					Comparator				
Model	Comparator	# patients	# ARF	person -months	IR (CI95%)	# patients	# ARF	person -months	IR (CI95%)	IRR (CI95%)
Unweighted	CBZ	45672,00	71	89259.87	7.95 (6.3, 10.04)	3914,00	4	7636.23	5.24 (1.97, 13.96)	1.52 (0.55, 4.16)
Weighted	CBZ	45612,29	69.38	89148	7.78 (6.16, 9.83)	2998,53	5.45	5859.32	9.3 (3.02, 28.65)	0.84 (0.27, 2.64)
Unweighted	GBP	45672,00	71	89259.87	7.95 (6.3, 10.04)	8208,00	22	16016.8	13.74 (9.04, 20.86)	0.58 (0.36, 0.93)
Weighted	GBP	45238,94	82.36	88334.07	9.32 (7.13, 12.2)	5780,97	10.91	11263.51	9.68 (5.51, 17)	0.96 (0.52, 1.8)
Unweighted	LTG	45672,00	71	89259.87	7.95 (6.3, 10.04)	9478,00	3	18527.5	1.62 (0.52, 5.02)	4.91 (1.55, 15.6)
Weighted	LTG	45536,62	62.82	88986.01	7.06 (5.59, 8.91)	8166,99	3.03	15954.72	1.9 (0.55, 6.58)	3.71 (1.05, 13.13)
Unweighted	OXC	45672,00	71	89259.87	7.95 (6.3, 10.04)	9005,00	2	17671.5	1.13 (0.28, 4.53)	7.03 (1.72, 28.65)
Weighted	OXC	45626,03	61.88	89238.72	6.93 (5.49, 8.75)	7517,26	3.12	14728.56	2.12 (0.43, 10.41)	3.27 (0.66, 16.35)
Unweighted	PHT	45672,00	71	89259.87	7.95 (6.3, 10.04)	7425,00	12	14446.63	8.31 (4.72, 14.63)	0.96 (0.52, 1.77)
Weighted	PHT	45483,73	79.75	88853	8.98 (7.03, 11.46)	5475,66	6.89	10649.35	6.47 (2.65, 15.83)	1.39 (0.55, 3.5)
Unweighted	TPM	45672,00	71	89259.87	7.95 (6.3, 10.04)	9287,00	9	18155.53	4.96 (2.58, 9.53)	1.6 (0.8, 3.21)
Weighted	TPM	45202,49	62.03	88301.03	7.02 (5.56, 8.87)	7790,25	7.58	15306.79	4.95 (1.53, 16.02)	1.42 (0.43, 4.69)
Unweighted	VPA	45672,00	71	89259.87	7.95 (6.3, 10.04)	9442,00	5	18490.63	2.7 (1.13, 6.5)	2.94 (1.19, 7.28)
Weighted	VPA	45296,58	65.62	88539.92	7.41 (5.85, 9.39)	8607,08	3.99	16862.56	2.37 (0.84, 6.69)	3.13 (1.08, 9.09)
Unweighted	**Monotherapy-overall**	**45672,00**	**71**	**89259.87**	**7.95 (6.3, 10.04)**	**64664,00**	**61**	**126399.9**	**4.83 (3.75, 6.2)**	**1.65 (1.17, 2.32)**
Weighted	**Monotherapy-Overall**	**44462,98**	**57.36**	**86865.75**	**6.6 (5.11, 8.54)**	**64472,25**	**66.23**	**126046 .06**	**5.25 (3.97, 6.96)**	**1.26 (0.86, 1.84)**
Unweighted	**Polytherapy**	**30426,00**	**36**	**59466.6**	**6.05 (4.37, 8.39)**	**65789,00**	**78**	**128663.33**	**6.06 (4.86, 7.57)**	**1 (0.67, 1.48)**
Weighted	**Polytherapy**	**29345,83**	**28.74**	**57340.44**	**5.01 (3.37, 7.44)**	**65671,29**	**83.23**	**128442 .05**	**6.48 (5.11, 8.21)**	**0.77 (0.49, 1.23)**

ARF=Acute renal failure; IR=Incidence rate; IRR=Incidence rate ratio; CI=Confidence interval;
CBZ=Carbamazepine, GBP=Gabapentin, LTG=Lamotrigine, OXC=Oxcarbazepine, PHT=Phenytoin, TPM=Topiramate, VPA=Valproic acid

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Table 20 Table of IRRs for ARF comparing levetiracetam group to other AEDs (Monotherapy and Polytherapy) Maximum Risk window 90 days. Baseline is the AED comparator (not levetiracetam)

		Levetiracetam				Comparator				
Model	Comparator	# patients	# ARF	person -months	IR (CI95%)	# patients	# ARF	person -months	IR (CI95%)	IRR (CI95%)
Unweighted	CBZ	45672,00	91	132211.53	6.88 (5.6, 8.45)	3914,00	5	11309.73	4.42 (1.84, 10.62)	1.56 (0.63, 3.83)
Weighted	CBZ	45606,10	87.93	132036.17	6.66 (5.42, 8.18)	2992,42	5.72	8670.84	6.59 (2.22, 19.55)	1.01 (0.33, 3.05)
Unweighted	GBP	45672,00	91	132211.53	6.88 (5.6, 8.45)	8208,00	32	23654.57	13.53 (9.57 , 19.13)	0.51 (0.34, 0.76)
Weighted	GBP	45270,40	103.18	130879.97	7.88 (6.28, 9.9)	5809,88	15.41	16737.82	9.2 (5.78, 14.67)	0.86 (0.51, 1.44)
Unweighted	LTG	45672,00	91	132211.53	6.88 (5.6, 8.45)	9478,00	5	27450.87	1.82 (0.76, 4.38)	3.78 (1.54, 9.3)
Weighted	LTG	45526,05	80.19	131763.72	6.09 (4.95, 7.48)	8170,33	9.12	23654.04	3.85 (1.46, 10.18)	1.58 (0.59, 4.26)
Unweighted	OXC	45672,00	91	132211.53	6.88 (5.6, 8.45)	9005,00	4	26245.37	1.52 (0.57, 4.06)	4.52 (1.66, 12.29)
Weighted	OXC	45625,57	79.2	132236.56	5.99 (4.87, 7.36)	7498,10	4.51	21804.85	2.07 (0.61, 7.02)	2.89 (0.84, 10)
Unweighted	PHT	45672,00	91	132211.53	6.88 (5.6, 8.45)	7425,00	21	21308.1	9.86 (6.43, 15.11)	0.7 (0.43, 1.12)
Weighted	PHT	45487,12	102.04	131577.21	7.76 (6.24, 9.64)	5455,97	11.2	15671.55	7.14 (3.65, 13.99)	1.09 (0.54, 2.2)
Unweighted	TPM	45672,00	91	132211.53	6.88 (5.6, 8.45)	9287,00	11	26877.33	4.09 (2.27, 7.39)	1.68 (0.9, 3.14)
Weighted	TPM	45224,27	80.08	130870.14	6.12 (4.97, 7.53)	7767,96	12.11	22625.09	5.35 (1.98, 14.49)	1.14 (0.41, 3.16)
Unweighted	VPA	45672,00	91	132211.53	6.88 (5.6, 8.45)	9442,00	9	27383.3	3.29 (1.71, 6.32)	2.09 (1.06, 4.15)
Weighted	VPA	45300,82	85.32	131172.38	6.5 (5.27, 8.03)	8589,67	11.75	24928.03	4.71 (2.12, 10.5)	1.38 (0.6, 3.16)
Unweighted	**Monotherapy-overall**	**45672,00**	**91**	**132211.53**	**6.88 (5.6, 8.45)**	**64664,00**	**93**	**187134.57**	**4.97 (4.06, 6.09)**	**1.38 (1.04, 1.85)**
Weighted	**Monotherapy-Overall**	**44515,57**	**74.02**	**128834 .19**	**5.75 (4.57, 7.22)**	**64461,83**	**102.67**	**186603 .92**	**5.5 (4.4, 6 .88)**	**1.04 (0.76, 1.44)**
Unweighted	**Polytherapy**	**30426,00**	**58**	**88105.13**	**6.58 (5.09, 8.52)**	**65789,00**	**108**	**190567.93**	**5.67 (4.69, 6.84)**	**1.16 (0.84, 1.6)**
Weighted	**Polytherapy**	**29341,60**	**50.09**	**84955.36**	**5.9 (4.33, 8.03)**	**65665,35**	**114.6**	**190199 .77**	**6.03 (4.92, 7.38)**	**0.98 (0.68, 1.42)**

ARF=Acute renal failure; IR=Incidence rate; IRR=Incidence rate ratio; CI=Confidence interval;
CBZ=Carbamazepine, GBP=Gabapentin, LTG=Lamotrigine, OXC=Oxcarbazepine, PHT=Phenytoin, TPM=Topiramate, VPA=Valproic acid

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