



The APAC-VALUE Study

: A global characterisation study of VALproate Utilisation and Exposure among men and women of childbearing age

Session 3 (May 7): Theory on Characterization and Treatment Pathways



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So what are we going to do?

The APAC-VALUE study: A global characterisation study of VALproate Utilisation and Exposure among men and women of childbearing age

- What: The OHDSI APAC community will embark on a collaborative large-scale federated network study examining the utilisation of valproate among men and women of childbearing age across diverse real-world data sources.
- Why: Valproate has long been an effective therapy for epilepsy, but growing global regulatory attention has highlighted the potential risks of neurodevelopmental disorders in children exposed in utero. While much of the focus has been on use in pregnancy, more recently several, but not all, regulatory agencies have issued safety warnings on the use of valproate in men prior to conception and neurodevelopmental risk in offspring.
- How: We aim to describe **utilisation patterns, trends, and population characteristics** to understand how safety warnings translate into real-world practice across different regulatory jurisdictions.



Scientific Forum May 7

Theory on characterization and treatment pathways

Community Call May 21

Review of treatment guidelines

Scientific Forum June 4

Framing the research question

Community Call June 18

Finalising the Protocol

Scientific Forum July 2

Building characterization and treatment pathways in ATLAS

Community Call July 16

Execution!

Scientific Forum August 6

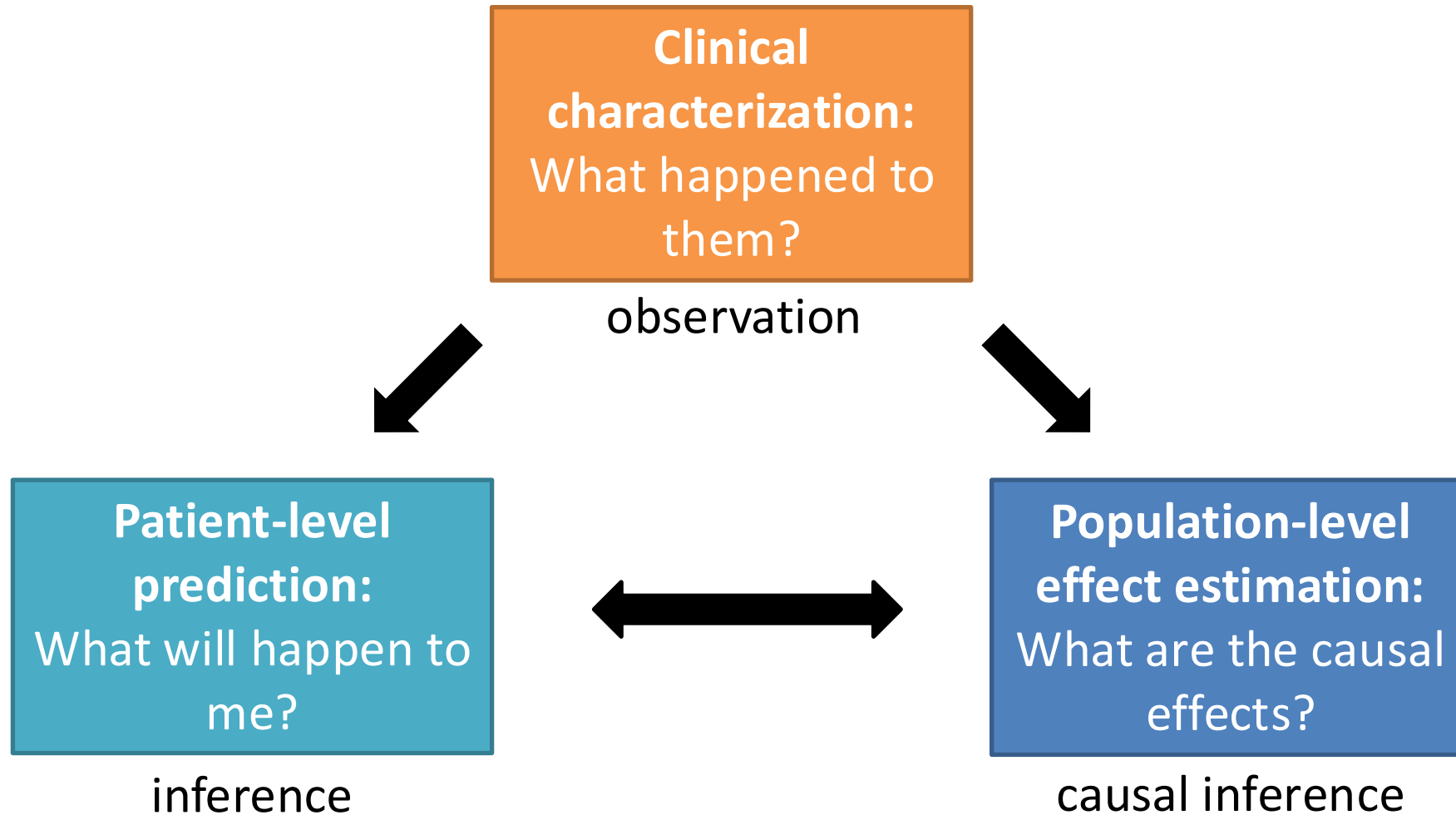
Introduction to Strategus

Community Call August 20

Interpreting the evidence

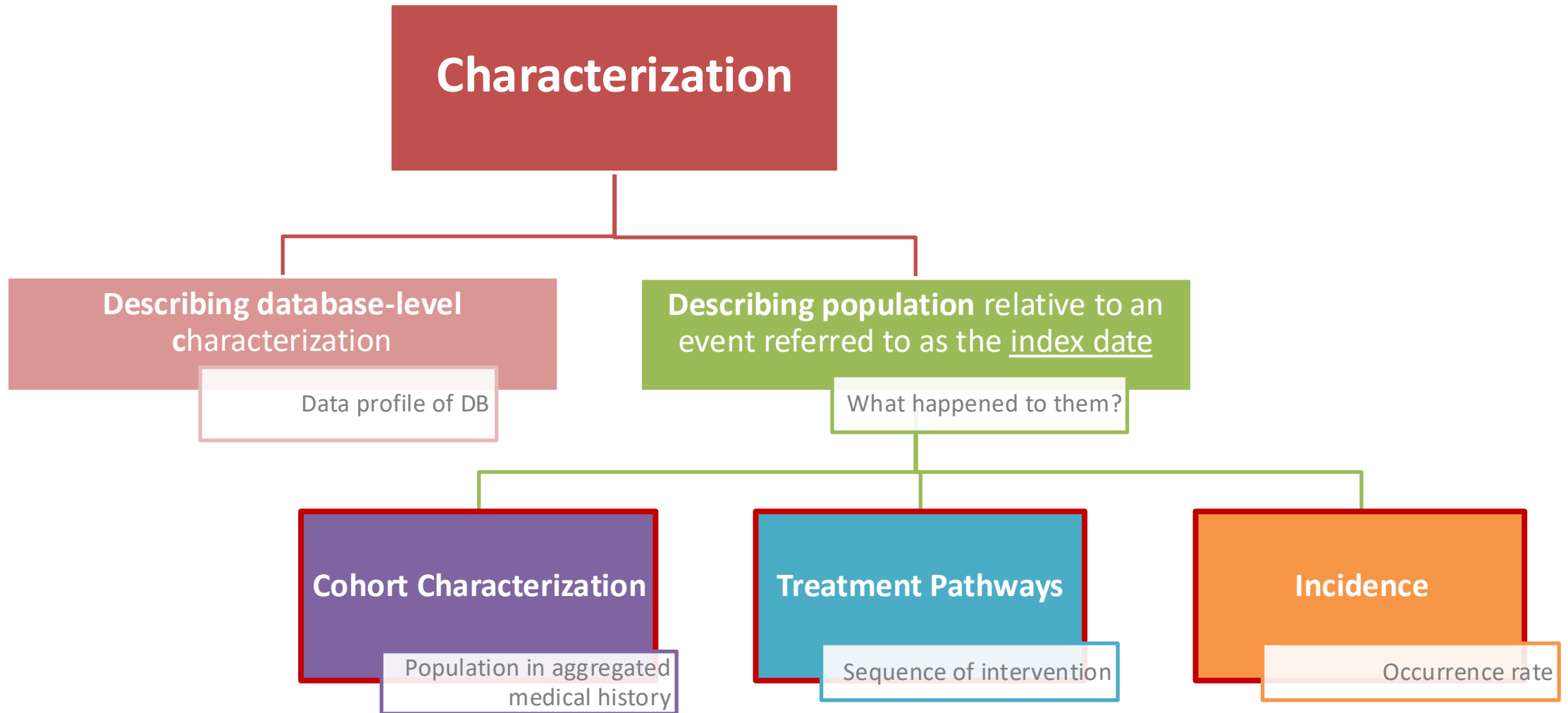


What type of questions can we ask?





1. What is Characterization





2. Why characterize?

- Characterization studies fill critical evidence gaps
 - Reveal disease natural history and real-world treatment utilization that RCTs can't capture
 - Expose variation in current clinical practice and quality of care
- They enable better downstream decisions:
 - Design RCTs grounded in real patient populations and treatment patterns
 - Inform treatment choice where head-to-head evidence is missing
 - Strengthen guideline updates and implementation in routine care



3. What do we need to define to run a pathway analysis?

Cohort Definition



Target Cohort

Cohort initiating a treatment, with a defined follow-up duration

Event Cohort



Index date = treatment initiation; end date = end of continuous exposure
Define one event cohort per treatment of interest



Analysis setting



Combination window

Treatments within window are merged



Minimum count

Drop pathways below threshold (privacy)



Max path length

How many sequential events to track



Treatment trajectories

Drug eras, switching, combination



Characterizing treatment pathways at scale using the OHDSI network

George Hripcsak^{a,b,c,1}, Patrick B. Ryan^{c,d}, Jon D. Duke^{c,e}, Nigam H. Shah^{c,f}, Rae Woong Park^{c,g}, Vojtech Huser^{c,h}, Marc A. Suchard^{c,i,j,k}, Martijn J. Schuemie^{c,d}, Frank J. DeFalco^{c,d}, Adler Perotte^{a,c}, Juan M. Banda^{c,f}, Christian G. Reich^{c,l}, Lisa M. Schilling^{c,m}, Michael E. Matheny^{c,n,o}, Daniella Meeker^{c,p,q}, Nicole Pratt^{c,r}, and David Madigan^{c,s}

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Hripcsak et al. 2016

Respiratory research

BMJ Open Respiratory Research

Real-world treatment trajectories of adults with newly diagnosed asthma or COPD

Aniek F Markus¹, Talita Duarte-Salles², Youngsoo Lee³, Daniel Prieto-Alhambra⁴, Guy G Brusselle⁵

Computer Methods and Programs in Biomedicine

TreatmentPatterns: An R package to facilitate the standard development and analysis of treatment patterns across domains

Aniek F. Markus^{1,*}, Katia M.C. Verhamme^{2,3}, Jan A. Kors⁴, Peter R. Rijn⁵

¹Department of Medical Informatics, Erasmus University Medical Center, Rotterdam, the Netherlands
²Department of Biomedicine, Ghent University, Ghent, Belgium

Markus et al. 2024

Pharmacoepidemiology and Drug Safety

WILEY

ORIGINAL ARTICLE OPEN ACCESS

Secular Trends in the Use of Valproate-Containing Medicines in Women of Childbearing Age in Europe: A Multinational DARWIN EU Network Study

Lucía Bellas^{1,2,3}, Martí Catalá¹, Edward Burn¹, Yuchen Guo¹, Mike Du¹, Katia Verhamme⁴, Egil Fridgeirsson⁴, Talita Duarte-Salles^{4,5}, Tommi Kauko⁶, Eeva Kronqvist⁶, James T. Brash⁷, Sarah Seager⁷, Daniel Prieto-Alhambra^{1,4}, Annika M. Jödicke¹, Albert Prats-Urbe¹

Bellas et al. 2025



A. Hripcsak et al., 2016 (1/4)

Research question

- For the same diagnosis, **which drug do clinicians actually choose first** — and how much does it differ across countries and data sources?

What was proposed

- Treat the sequence of medication after diagnosis— the **treatment pathway**, not just a description — as a unit of large-scale observational study.

Scope

- Three chronic conditions: hypertension, type 2 diabetes, depression.
- 11 OHDSI databases (US claims, EU primary care, hospital EHR), ~250M patients.

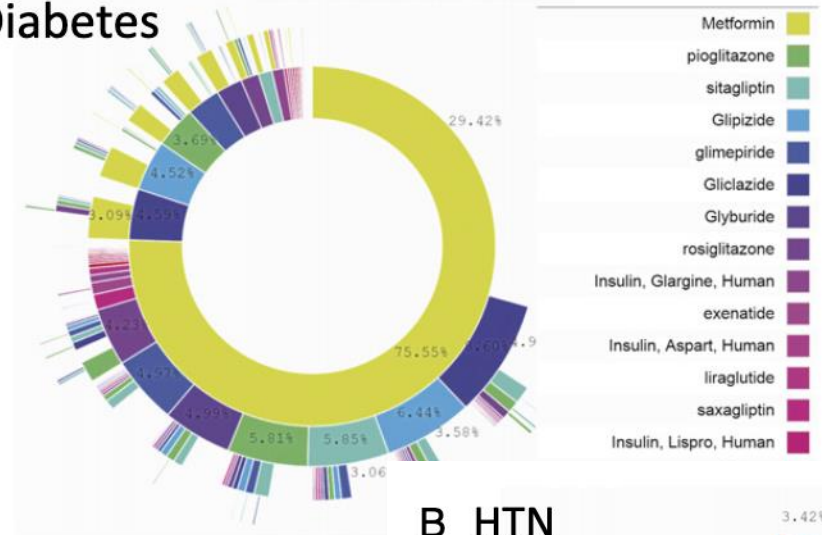


A. Hripcsak et al., 2016 (2/4)

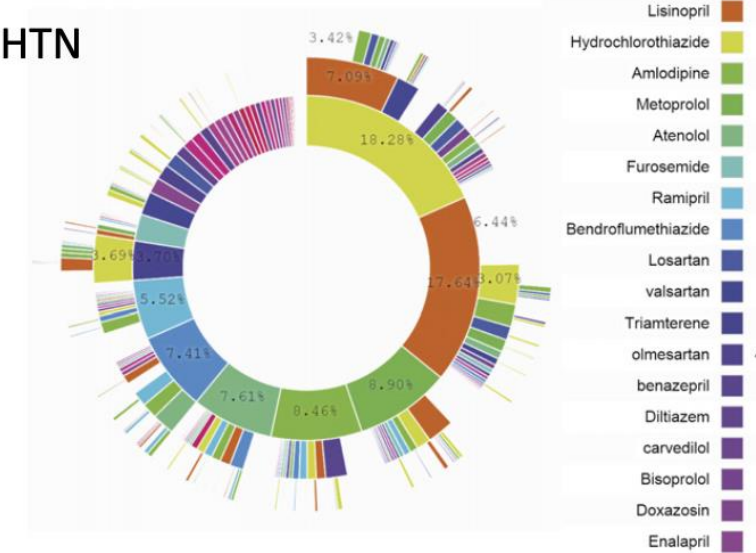
Findings

- **T2DM:** metformin first-line across all 11 DBs.
- **HTN & depression:** first-line varies sharply — largest in depression.
- *10% of diabetes patients, 24% of hypertension patients, and 11% of depression patients followed a treatment pathway shared with no one else*

A Diabetes



B HTN



Reading the sunburst: inner ring = first drug; outer rings = next in sequence. Arc width = patient share.



A. Hripcsak et al., 2016 (3/4)

Interpretation

- T2DM; strong guideline → uniform practice (T2DM).
- Hypertension & depression; weaker consensus → multiple drug classes are considered acceptable first-line options, local culture & formulary dominate.

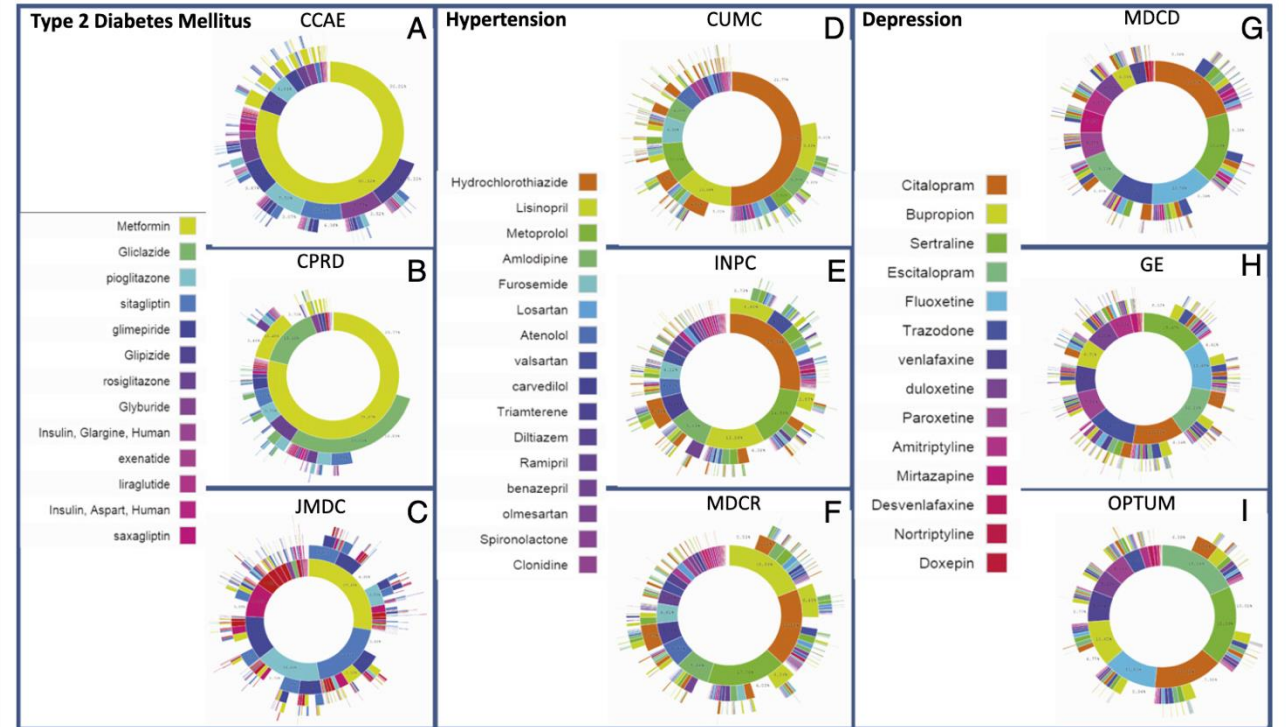


Fig. 3. For each disease, diabetes (A–C), hypertension (D–F), and depression (G–I), the inner circle shows the first relevant medication that the patient took, the second circle shows the second medication, and so forth. Three data sources are shown for each disease; the data source abbreviations are defined in Table 2.



A. Hripcsak et al., 2016 (4/4)

Medication-use metrics over calendar years

- Each panel: a per-DB metric tracked across years.
- Share switching from monotherapy, share initiating with the most common drug — complementary to the first-line view.

What the trends show

- Switching and discontinuation are non-trivial and site-specific.
- Persistence on initial therapy varies more than first-line choice itself.
- Calendar trends shift even without new guidelines.

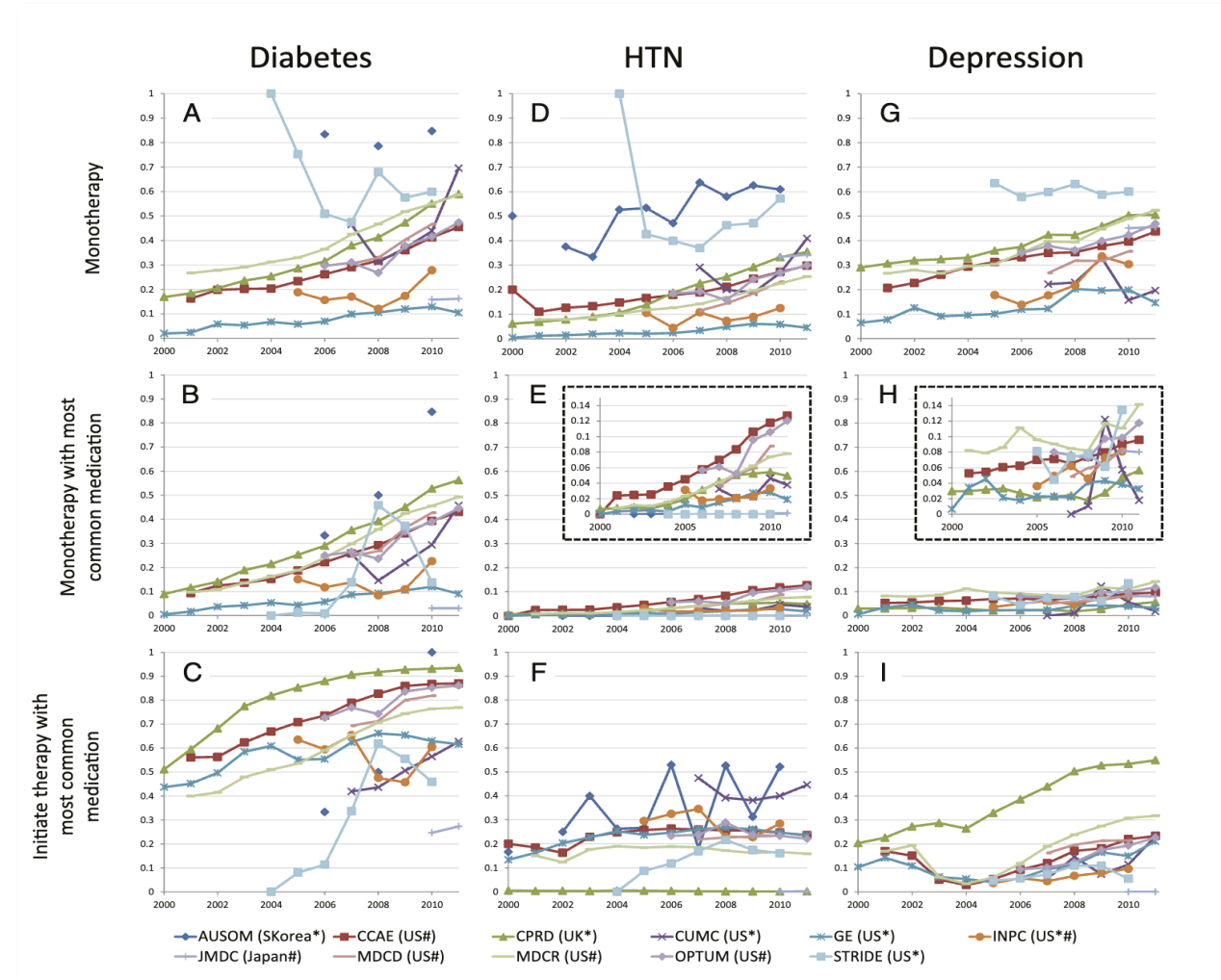


Fig. 5. Medication-use metrics by data source.



B. Markus et al., 2024 (1/3)

Research question

- For asthma/COPD, **how does treatment evolve after diagnosis** — step-up, step-down, switching, discontinuation — and how do these dynamics differ across countries and data sources?

GINA/GOLD prescribe step-up, step-down, and ICS+LABA(+LAMA) combinations as standard care — so trajectory dynamics are the question

Scope

- Applied to newly diagnosed adults with asthma or COPD across 7 databases.



B. Markus et al., 2024 (2/3)

What was measured

- Beyond first-line choice: step-up, step-down, switching, and discontinuation as comparable, per-database rates.
- Table 3 (right) — asthma: switching 8–28%, step-up 12–24%, step-down 7–23%, no-follow-up 19–38% across 7 sites.

Table 3 Percentage of adults with asthma who switched, stepped-down or stepped-up respiratory pharmacological treatment after the first-line treatment (broad definition)

Label	CCAЕ (USA)	Medicaid (USA)	Medicare (USA)	EHIF (Estonia)	CPRD (UK)	SIDIAP (Spain)	IPCI (The Netherlands)	AUSOM (South Korea)
Step-up	13.1	11.9	12.0	20.6	23.9	21.0	17.6	14.3
Step-down	9.0	6.6	7.7	23.0	16.7	17.5	9.9	19.5
Switching	9.7	7.9	9.5	11.8	27.8	17.2	11.2	6.0
Start of acute exacerbation	20.1	20.9	18.3	10.6	6.5	12.4	12.1	14.3
End of acute exacerbation	15.9	14.9	15.9	3.3	4.6	8.4	8.1	14.9
No follow-up treatment*	32.0	37.5	36.0	29.9	19.1	20.6	38.4	30.6
Other	0.2	0.3	0.5	0.8	1.4	2.8	2.7	0.4

*Patients who did not receive medication of a different respiratory drug class after the first treatment, that is, patients who remained on the same treatment or who discontinued treatment.



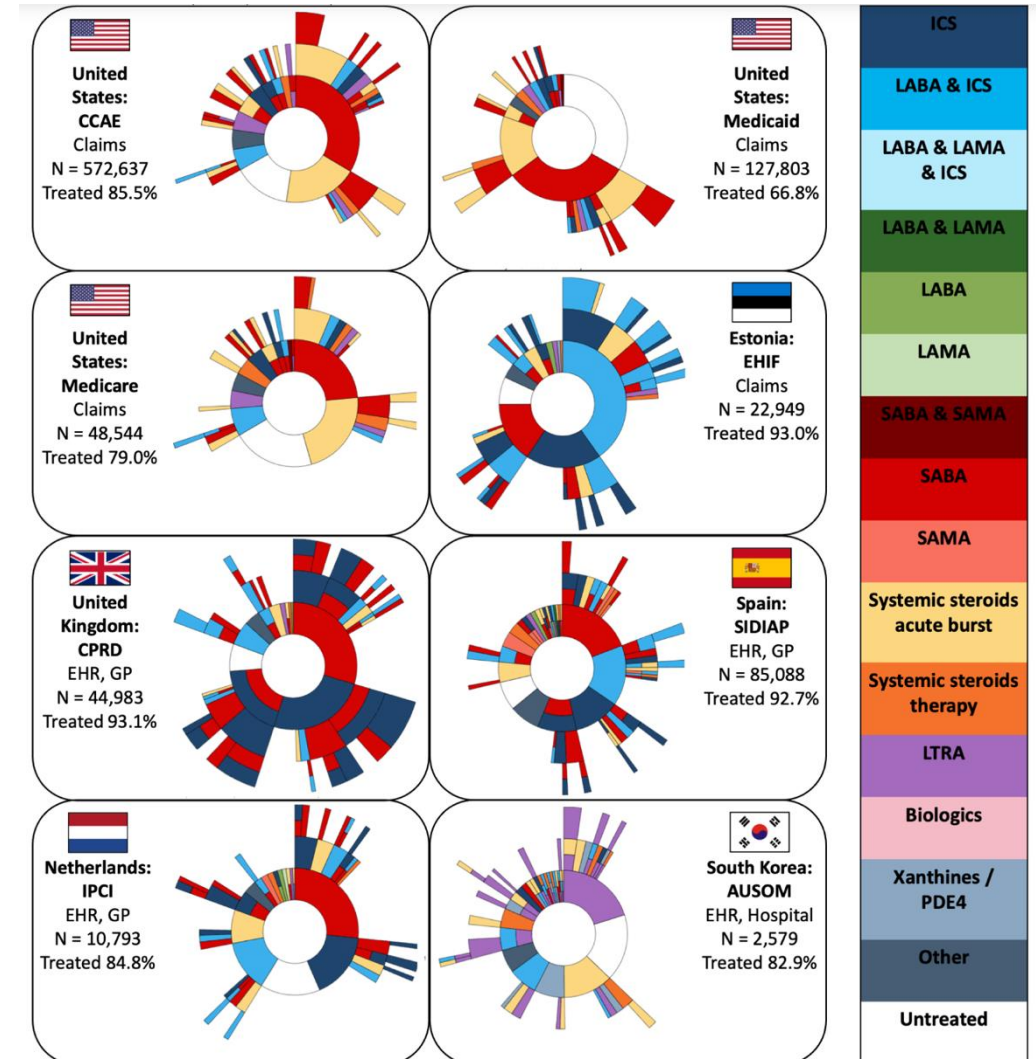
B. Markus et al., 2024 (3/3)

What stands out

- First-line choice differs sharply by country: ICS-based regimens dominate in some sites, LAMA or LABA monotherapy in others.
- Outer rings show frequent switching and add-on therapy within the first year — pathways are rarely linear.

Interpretation

- Differences reflect **formulary, reimbursement, and prescribing culture** — not patient mix alone.





Why this study is relevant here


- Same drug (valproate), same population concern (women of childbearing age), same OHDSI / OMOP-CDM lineage
- Conducted as a DARWIN EU network study commissioned by the European Medicines Agency

What it does (and does not) cover

- Estimates secular trends in incidence and prevalence of VPA and alternative antiepileptics in young women across 8 European databases (NL, ES, UK, BE, DE, FI).
- Drug utilization study — reports what is prescribed, not full treatment pathways or sequencing.

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Keywords: antiepileptic drugs | drug utilization | network study | pharmacoepidemiology

ABSTRACT

Background: Valproate-containing medicines (VPA) are first-line treatments for epilepsy; however, they pose teratogenic risks, restricting their use in women of childbearing age. We aimed to estimate the secular trends in the use of VPA and alternative treatments in young women, and to characterise dose/strength, treatment duration, and indication in new VPA users.

Methods: We conducted a multi-national population-based cohort study using primary care records from the Netherlands, Spain, and the UK (IPCI, SIDIAP, CPRD GOLD), primary and outpatient specialist care records from Germany and Belgium (IQVIA DA Germany, IQVIA LPD Belgium), and hospital records from Finland (ACI VARHA), all mapped to the OMOP Common data



C. Bellas et al., 2025 (2/2)

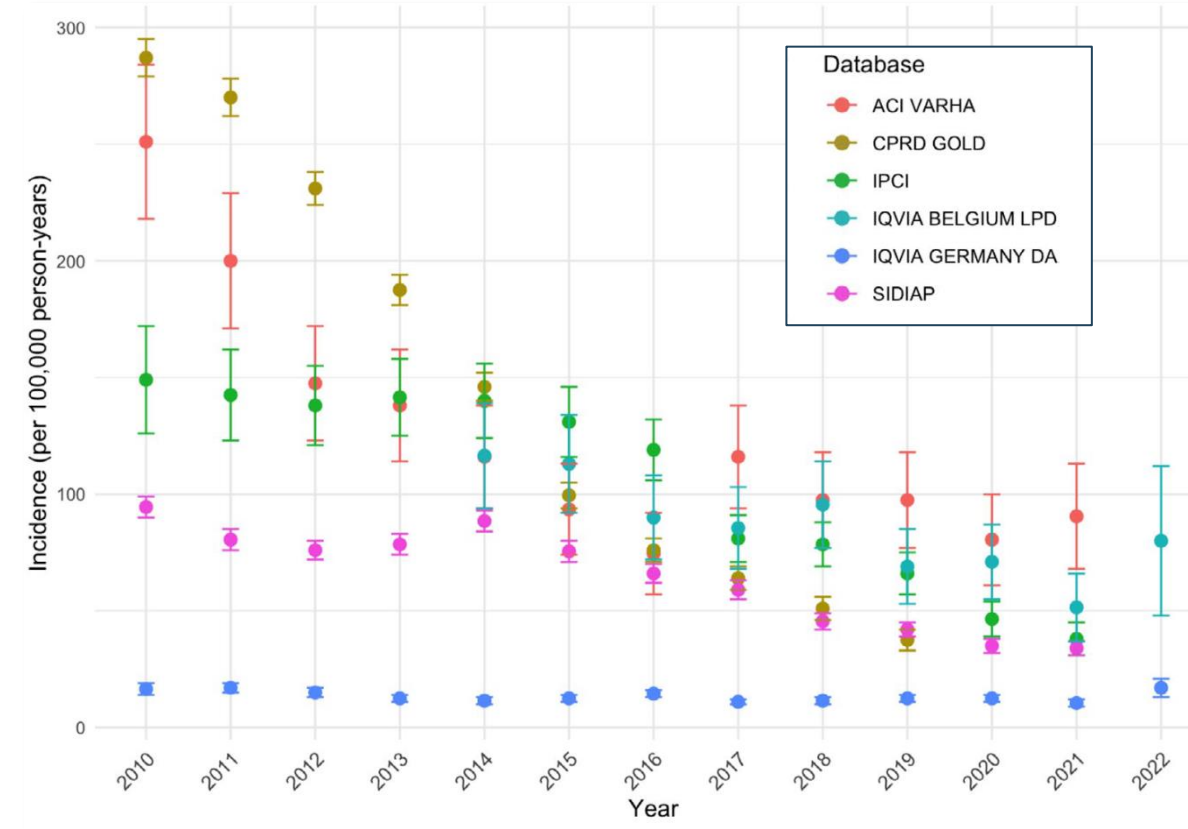


FIGURE 1 | Annual incidence rates of VPA use in women aged between 12 and 55 years in 2010–2022.

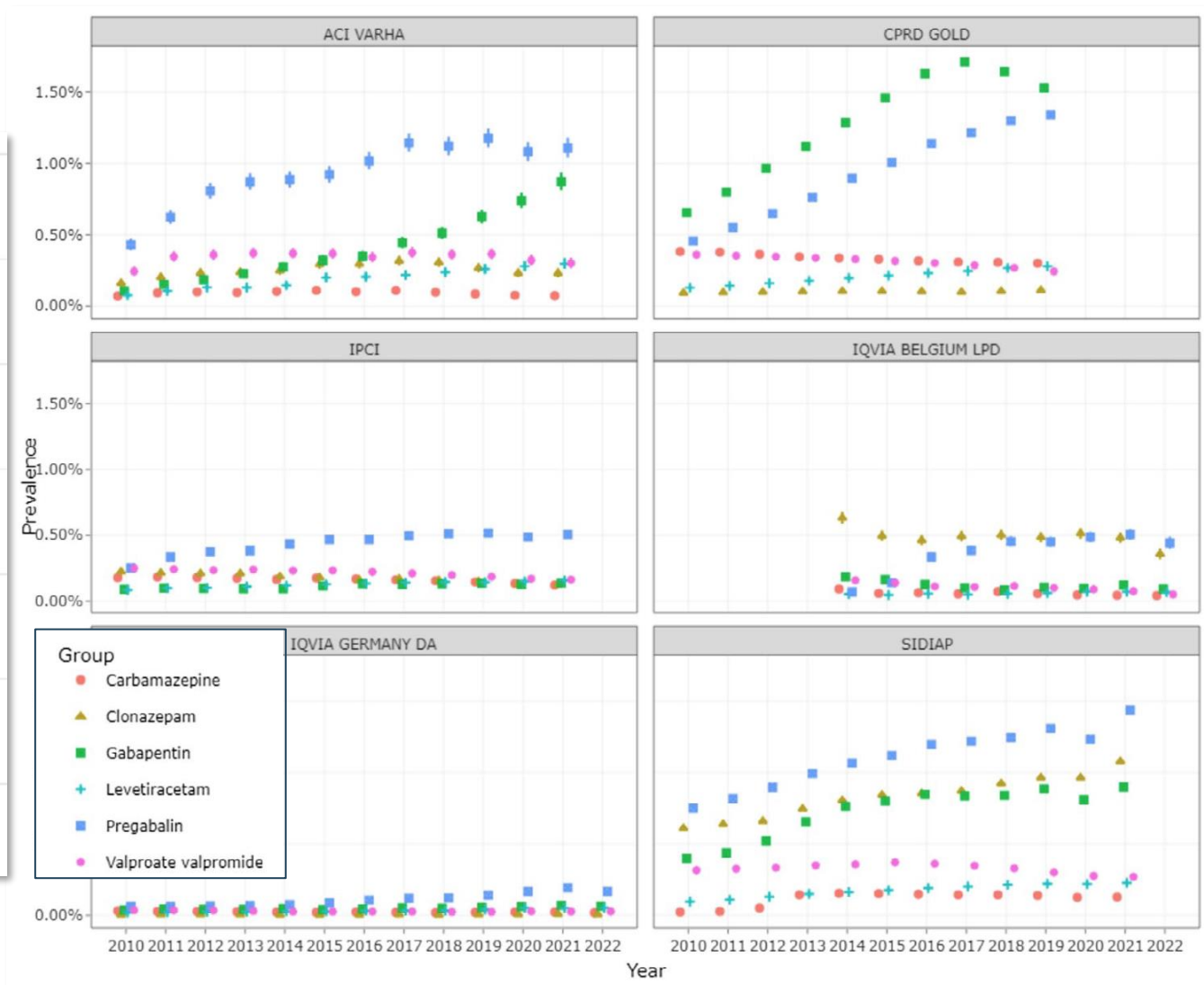


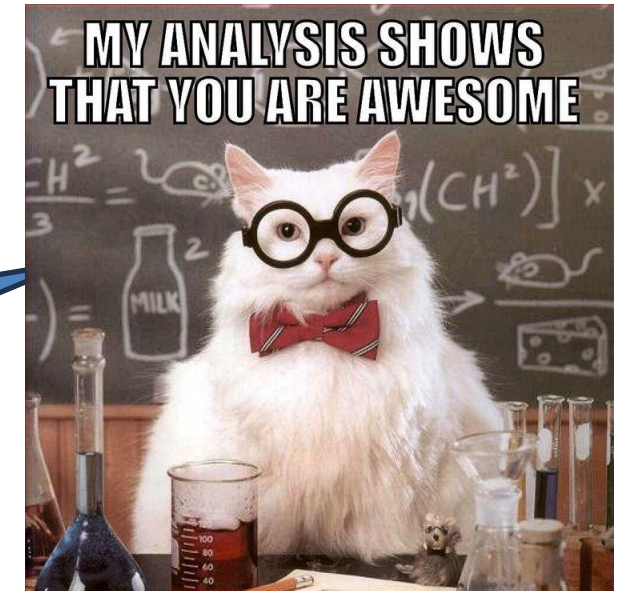
FIGURE 3 | Prevalence of VPA and the 5 most used alternative treatments in women aged between 12 and 55 years in 2010–2022.



Take away message

- **Characterization and Treatment Pathways give you:**
 1. Cohort characteristics
 2. Treatment diversity
 3. Treatment sequences
 4. Adherence to guidelines
- But the design must follow the question:
 - **The unit of analysis should mirror the unit of clinical decision** (*First exposure, drug era, or population trend*)

Join us in APAC
VALUE study!





April 2026
Kick-Off

May 2026
Preparation

- ✓ Characterisation & Treatment Pathways
- ✓ Setting the Scene for our Study

June 2026
Framing the Research Question

- ✓ Cohort Development
- ✓ Protocol Design

July 2026
Building

- ✓ Creating & Execution of Analysis

August 2026
Interpretation

- ✓ Interpreting & Communicating the Results

Homework: Review treatment guidelines and Regulatory Agency warnings in your Region

Chat 2026 APAC-VALUE Study Posts Shared

Unread Channels Chats Meeting chats

Copilot

Teams and channels

- OHDSI
 - General
 - GDE2025 - Antiplatelet use in ACS und...
 - GDE2025 - Bladder cancer treatment
 - GDE2025 - Obesity management
 - GDE2025 - Ulcerative colitis treatment...
 - Teams Best Practices and Guidance
 - Teams Technical support
- Workgroup - OHDSI APAC Steering Comm...
 - General
- OHDSI APAC
 - General
 - 2022 APAC Study 1 (CHAPTER)
 - 2022 APAC Study 2 (ACESO_Long COVID)
 - 2022 APAC Study 3 (Multiple Sclerosis)
 - 2022 APAC Study 4 (Data Quality of APAC)
 - 2024 APAC ETL Project
 - 2024 APAC ETL Project - Data Analysis
 - 2024 APAC ETL Project - ETL
 - 2024 APAC ETL Project - Quality Assur...
 - 2024 APAC ETL Project - Vocabulary Map...
 - APAC Scientific Forum

See all channels

GL Gaeun Lee 27/03 10:56 am

Study Overview

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Valproate has long been an effective therapy for epilepsy, but growing global regulatory attention has highlighted the potential risks of neurodevelopmental disorders in children exposed in utero. While much of the focus has been on use in pregnancy, more recently several, but not all, regulatory agencies have issued safety warnings on the use [see more](#)

Reply in thread

[Review of Guidelines and Warnings.xlsx](#)