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# Benefits of Inhaled Corticosteroids (ICS) in COPD maintenance combinations

## Real-world evidence using Longitudinal Targeted Maximum Likelihood Estimation (L-TMLE)

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# Background

- Chronic Obstructive Pulmonary Disease (COPD) has been characterized as a complex disease affecting patients' health beyond the lungs.
- Combination therapy involving inhaled corticosteroids (ICS) and long-acting bronchodilators is recommended for symptomatic COPD patients with frequent exacerbations.
- Pivotal RCTs have shown lower exacerbation rates with ICS-containing therapy compared to non-ICS containing therapies.
- However, there is need for evidence of benefit in diverse patient populations
  - ➢ Some recent RWE studies failed to replicate the benefits seen in RCTs.
  - ➢ Reasons for this may include among others
    - Inadequate data on confounders
    - Use of non-robust analysis methods.

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**Advances in causal inference methods**

e.g. Double robust TMLE

+

**Rich linkable datasets**

- Province wide (Alberta, Canada)
- 4.5+ million individuals

## Opportunity

- ❑ Real-world evidence on the benefits of ICS in a diverse patient population

# Available Real-World Data| Alberta - Canada

## Health Services Data

- ✓ Hospitalizations
- ✓ Ambulatory care visits
- ✓ Physician claims
- ✓ Diagnosis and procedure codes
- ✓ Length of stay


## Lab Data

- ✓ Test name, date, results
- ✓ Abnormal diagnosis
- ✓ Reason for test
- ✓ IHC/cytopathology

## Drug Data

- ✓ Private and public plan claims
- ✓ Drug names
- ✓ Medication Possession Ratio
- ✓ Proportion of Days Covered
- ✓ Gaps in treatment
- ✓ Treatment switching
- ✓ Concomitant medication use

## Alberta Cancer Registry

- ✓ Patient demographics
- ✓ Tumour information
  - Site and stage at diagnosis
  - Topography and morphology
- ✓ Initial cancer treatment

## Vital Statistics

- ✓ Births/Deaths
- ✓ Marriage
- ✓ Gender and geographic Information

Alberta Health Services

Alberta Health

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# Study Objectives

- To estimate the effect of an ICS-containing COPD maintenance therapy on the rates of exacerbations in the 1 year following initiation of COPD maintenance.
- To assess the feasibility of using available administrative data and double-robust causal inference methods to obtain reliable RWE.

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# Study Design

- Longitudinal cohort study using routinely-collected data from Alberta Health

- Source population
  - Alberta Health's COPD chronic disease cohort
- Inclusion criteria
  - First met the COPD diagnosis algorithm between April 1, 2014, to March 31, 2019
  - ≥40 years old at COPD diagnosis
  - Initiated a long-acting COPD maintenance therapy at any time after diagnosis
    - ➢ follow up was started at the first dispense of a long-acting COPD maintenance therapy

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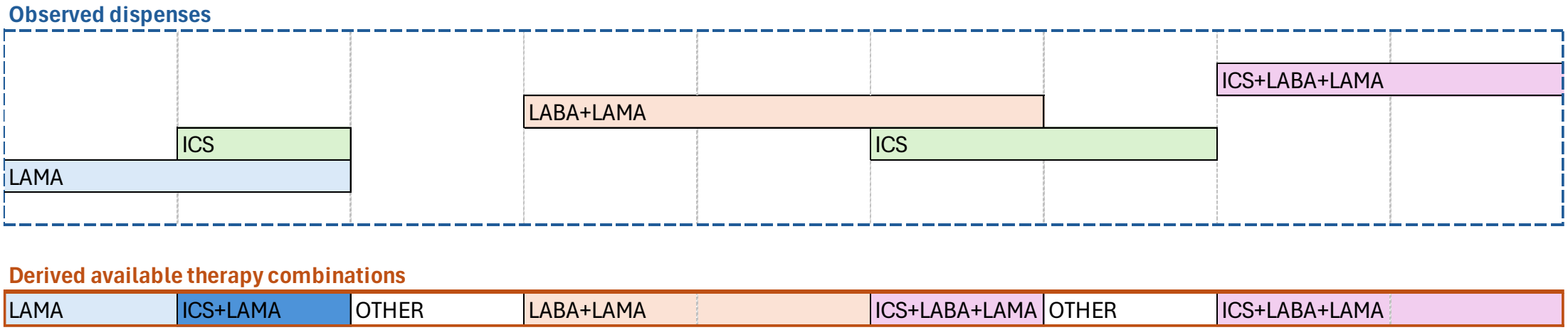
# Exposure Definition




1. ICS+LABA+LAMA
2. LABA+LAMA
3. OTHER

**Abbreviations**

| | |
|---|---|
| ICS | Inhaled corticosteroid |
| LABA | Long-acting beta agonist |
| LAMA | Long-acting muscarinic antagonist |

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# Outcome Definition

## Exacerbation

### Moderate exacerbation of COPD

A physician outpatient visit with

- ❑ A diagnosis ICD-9 code for “COPD” (491, 492, 496)

  **AND**

- ❑ New dispensation of Oral corticosteroids (OCS ) within 5 days of the visit (before or after) and dosage of 20-60 mg per day , **or** Antibiotics for respiratory infections within 5 days of the visit (before or after) and for a duration <15 days

### Severe exacerbation of COPD

- ❑ An emergency department (ED) visit with a COPD diagnosis (J41-J44) in any position

  **OR**

- ❑ hospitalization with a “most responsible diagnosis” (reason for admission) code or post-admission diagnosis for COPD (J41-J44)

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# Potential Confounders

**Identified in consultation with Clinical advisors**

**Baseline**

- ❑ Demographic characteristics
- ❑ Calendar year at therapy initiation
- ❑ Time from diagnosis to therapy initiation

**Time varying**

- ❑ Comorbidities
- ❑ COPD Severity measures/proxies
- ❑ Prior treatments

+

**Additional variables:**
**12 months prior to therapy initiation**

**Baseline**

- ❑ Each ICD 10 diagnosis code group that appeared as
  - ➢ Main reason for admission or visit to emergency department
  - ➢ Occurring during admission.
- ❑ All the intervention procedures occurring during admission or visit to emergency department
- ✓ Included those occurring in at least 0.5% of the study patients

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# Statistical Analysis

Because patients can switch from one therapy to another in the 1 year of follow-up.

- Longitudinal model
  - 1-year follow-up divided into 15-day time intervals
  - Used an intention to treat analysis approach, in which the first long-acting therapy combination in each interval was taken as the treatment for the interval

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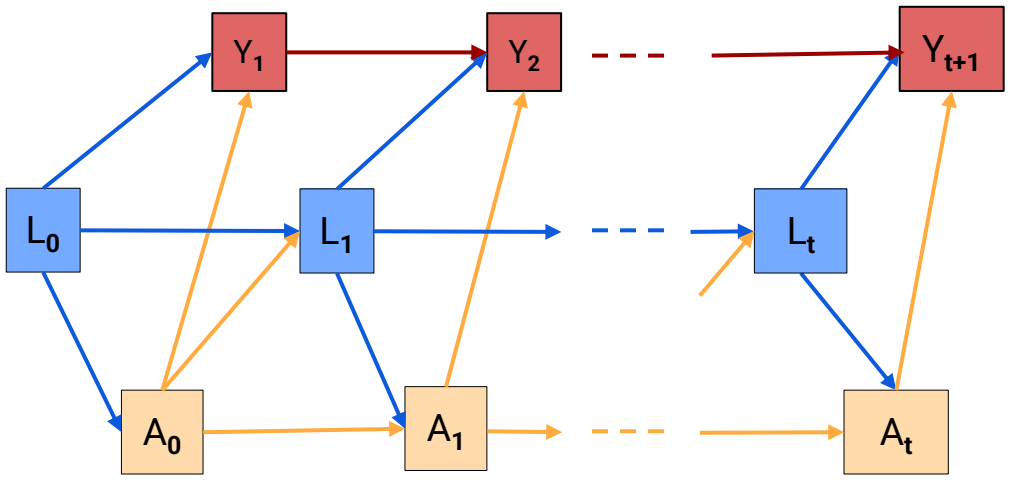
# Statistical Analysis




***Note**: Though not shown for simplicity*
- ❑ *Censoring nodes were also included.*
- ❑ *For each node, all the preceding nodes were considered parents*

**Y: COPD exacerbations**

**Confounders**

**Baseline covariates: $L_0$**

e.g Age, sex, SES (Neighborhood average income), year at Long-acting therapy initiation, time from COPD diagnosis to therapy initiation + Additional variables

**Time-varying: $L_t$**

- Comorbidities (e.g Diabetes type-2, Pulmonary oedema, etc. )
- COPD severity(e.g #Exacerbations in past 12 months)
- COPD treatments in past 12 months
- Hospitalizations in past 12 month
- Outpatient physician visits in pas 12 month
- Long-acting treatment combination in prior 12 months

**A: Long-acting treatment**

1. ICS+LABA+LAMA
2. LABA+LAMA
3. OTHER

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# Statistical Analysis

## Causal parameter of interest

Marginal mean difference in the rates of exacerbations if all patients received

**ICS+LABA+LAMA** ($\bar{a}_1$) in all the intervals they were followed up

VS

**LABA+LAMA** ($\bar{a}_0$) in all the intervals they were followed up.

$$\boldsymbol{\psi_{causal} = E(Y_{\bar{a}_1}) - E(Y_{\bar{a}_0})}$$

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# Estimation

Estimation of the causal parameter of interests from observed data, $\psi_{observed}$

- Was carried out using an extension of TMLE for longitudinal data (L-TMLE), which is available in an R-package ***ltmle.***

Lendle SD, Schwab J, Petersen ML, van der Laan MJ (2017). **ltmle**: An R Package Implementing Targeted Minimum Loss-Based Estimation for Longitudinal Data. *Journal of Statistical Software*, 81(1), 1–21. doi:10.18637/jss.v081.i01.

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# Estimation

The L-TMLE implementation involves estimation of

- Treatment assignment mechanism
- Censoring mechanism (as we could not assume non-informative censoring)
- Sequential regressions for the outcome
  - With a targeting step after each regression using a clever covariate or weight(as implemented in the ***ltmle*** package)

- All the three components were estimated using the **superlearner** algorithm.

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# Estimation - Superlearner

- In the current analysis, 4 machine learning algorithms were included as candidates in the *superlearner* library
    1. Feed-forward neural networks with a single hidden layer (*SL.nnet*)
    2. Extreme Gradient Boosting (*SL.xgbost*)
    3. Generalized Additive Models (*SL.gam*)
    4. Generalized Linear Models (*SL.glm*)
- Each algorithm was paired with a correlation test screener(*screen.corP*), with minPvalue parameter of 0.05.

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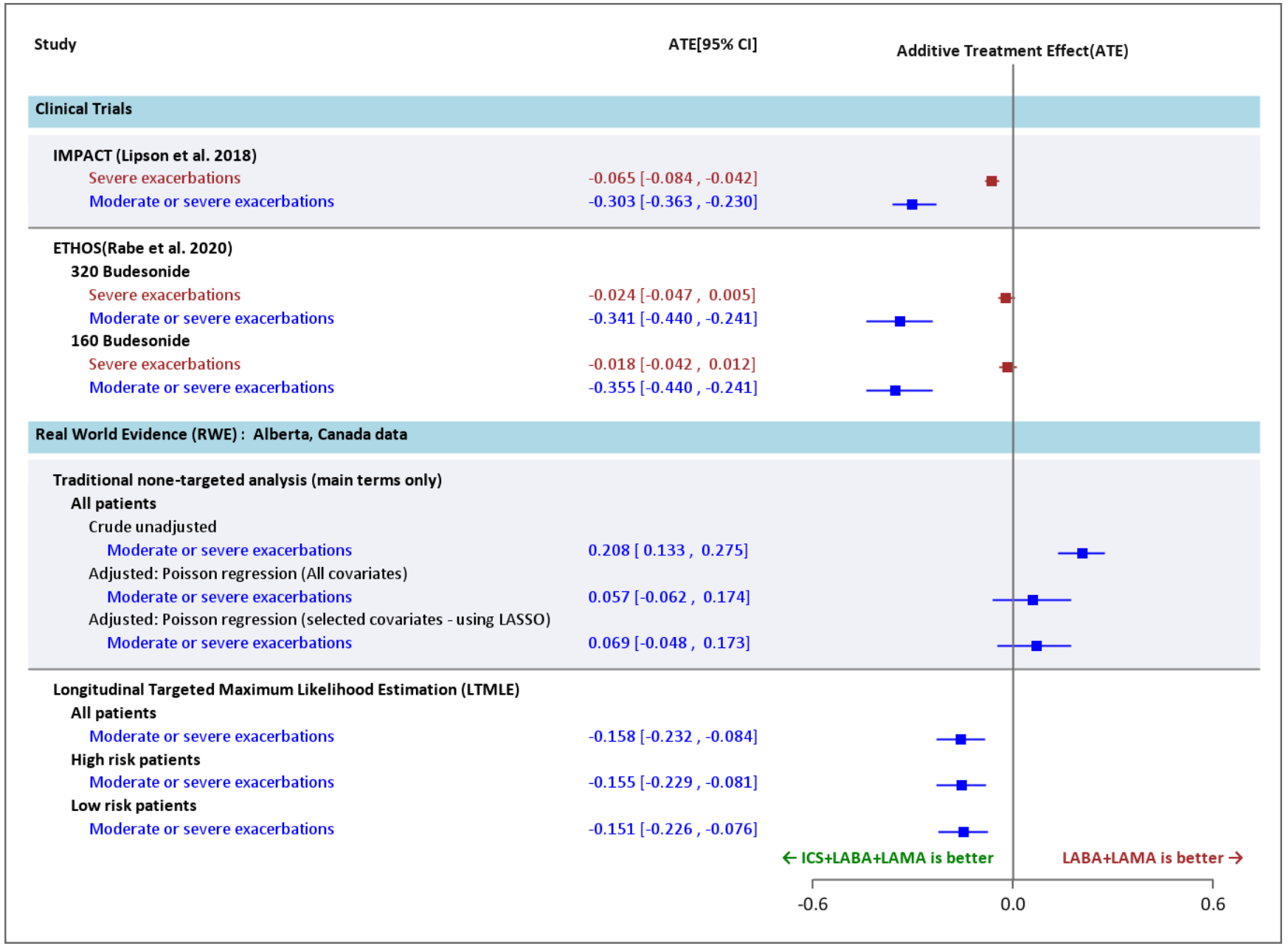
# Preliminary Results

**N = 11,839 patients**

28% High risk category

## ICS+LABA+LAMA vs LABA+LAMA



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# Limitations

- The treatment definition is based on only the availability of medication given the dispense dates and the number of days each supply was intended to cover and NOT the actual use of the dispensed medication.
  - It is possible patients may not use the dispensed medication within the supply days
  - But instead use it in later time intervals

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# Conclusion

- These preliminary results show a benefit of ICS+LABA+LAMA over LABA+LAMA for both:
  - High risk COPD patients,  as shown in RCTs
  - Low risk COPD patients, who were not included in the RCTs.

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# Next Steps

- ❑ Add mortality analysis
- ❑ Add  sensitivity analysis - outcome blind simulations
- ❑ Explore other machine learning algorithms/screeners and parameter tuning