OHDSI RA/TOFA study proposal, short version:

Objectives: 1) to compare the risk of TOFA vs. ETN, TOFA vs. ADA for MACE in moderate to severe RA. 2) to compare the evidence generated from OHDSI observational study to evidence generated from the future phase 4 RCT results.

Methods: This is a retrospective study using xx claim data and xx EHR data.

1, Participants: patients > 18 yo, with moderate to severe RA who were newly started on ETN, ADA or TOFA (index date), defined by

1. one **RA code** + one **medication code for ETN, ADA or TOFA**.
2. Has a 6-12 months of run-in period before the index data
3. No biologics were prescribed during the run-in period (this means patients escalating their therapy from non-biologics, to ensure the three cohorts are comparable; this is also help to address the question that if a patient had exposures to all three medications, in this case, we will only include the first exposure. But it may significantly limit sample size for TOFA)
4. **Exclusion codes:** psoriasis, psoriatic arthritis, ankylosing spondylitis, lupus, crohn’s disease, ulcerative colitis, uveitis (these diagnoses are also associated with use of ETN, ADA or TOFA)

2, Intervention: TOFA, all dosages

3, Comparator: ETN, ADA

4, Outcomes: Time to Event (= “on treatment” analysis).

A, Time 0: index date, the first date that ETN, ADA, or TOFA was prescribed/dispensed.

B, Event: **Major Adverse Cardiac Events (MACE)**, including non-fatal MI, non-fatal stroke, death from cardiovascular causes.

Suggestion: Use LEGEND AMI and stroke definitions

### Acute myocardial infarction

Initial Event Cohort

People having any of the following: 

* a condition occurrence of Acute MI1
  + for the first time in the person's history
  + condition type is any of: Inpatient detail - primary, Inpatient header - primary, Primary Condition, Inpatient detail - 1st position, Inpatient header - 1st position
  + visit occurrence is any of: Emergency Room Visit, Inpatient Visit

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **earliest event per person.**

Limit qualifying cohort to: **earliest event per person.**

No end date strategy selected. By default, the cohort end date will be the end of the observation period that contains the index event.

Appendix 1: Concept Set Definitions

1. Acute MI

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 4329847 | Myocardial infarction | Condition | SNOMED | NO | YES | NO |
| 314666 | Old myocardial infarction | Condition | SNOMED | YES | YES | NO |

### Stroke

Initial Event Cohort

People having any of the following:

* a condition occurrence of Stroke (ischemic or hemorrhagic)2

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **all events per person.**

For people matching the Primary Events, include:

Having any of the following criteria:

* at least 1 occurrences of a visit occurrence of Inpatient or ER visit1

where event starts between all days Before and 1 days After index start date and event ends between 0 days Before and all days After index start date

Limit cohort of initial events to: **all events per person.**

Limit qualifying cohort to: **all events per person.**

End Date Strategy

Date Offset Exit Criteria

This cohort defintion end date will be the index event's start date plus 7 days

Cohort Collapse Strategy:

Collapse cohort by era with a gap size of 180 days.

Appendix 1: Concept Set Definitions

1. Inpatient or ER visit

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| 262 | Emergency Room and Inpatient Visit | Visit | Visit | NO | YES | NO |
| 9203 | Emergency Room Visit | Visit | Visit | NO | YES | NO |
| 9201 | Inpatient Visit | Visit | Visit | NO | YES | NO |

2. Stroke (ischemic or hemorrhagic)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| 372924 | Cerebral artery occlusion | Condition | SNOMED | NO | NO | NO |
| 375557 | Cerebral embolism | Condition | SNOMED | NO | NO | NO |
| 376713 | Cerebral hemorrhage | Condition | SNOMED | NO | NO | NO |
| 443454 | Cerebral infarction | Condition | SNOMED | NO | YES | NO |
| 441874 | Cerebral thrombosis | Condition | SNOMED | NO | NO | NO |
| 439847 | Intracranial hemorrhage | Condition | SNOMED | NO | NO | NO |
| 432923 | Subarachnoid hemorrhage | Condition | SNOMED | NO | NO | NO |

C, Censored: patients who exit the data source, discontinue the studied drug (defined by a **different biologics** was prescribed/dispensed, or 60-90 days after the last dispense of the study drug, whichever comes first.)

5, Analysis:

With **Negative outcomes**.

Survival analysis with propensity scores. Report as Cox Proportional Hazard Ratio.

Sensitivity analysis: “Intent-to-treat”, index date to the date of exit cohort.

Code sets: bolded.