Comparative effectiveness of ACE inhibitors vs. angiotensin receptor blockers to prevent or delay dementia: a target trial emulation using US electronic health records

SESSTIM Webinar
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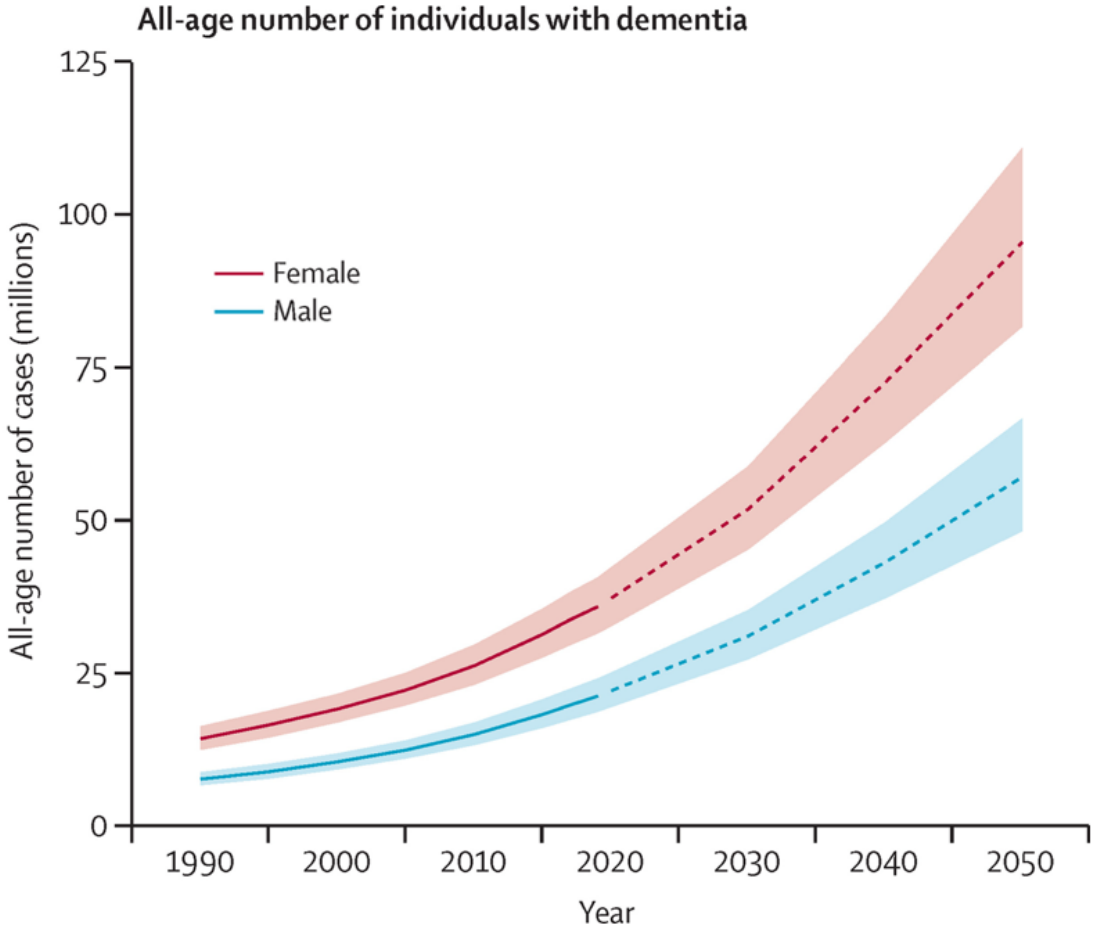
November 21, 2025

Motivation: the growing burden of dementia

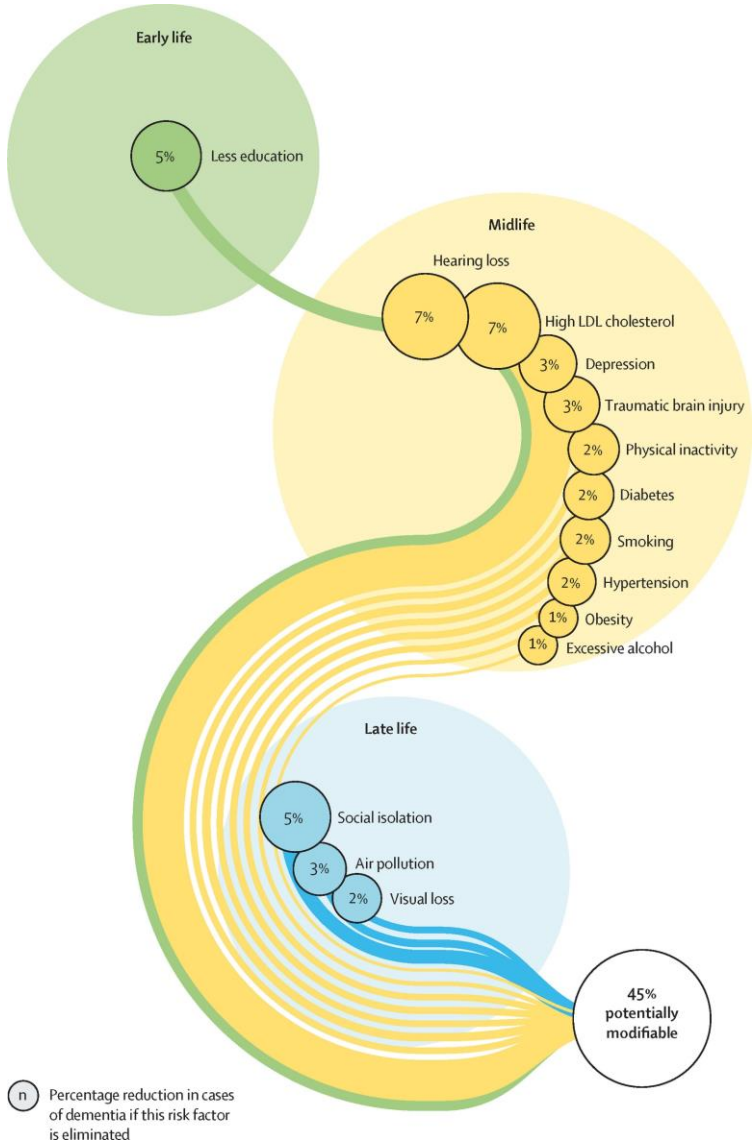
- 55 million people affected by dementia globally.
- Expected increase of 1.4-fold by 2030 and 2.5-fold by 2050.
- Modest cognitive benefits of Leqembi, but serious risks (e.g., >10% brain edema or hemorrhage).



Sources: [2022 Alzheimer's disease facts and figures](), [Global Burden of Disease Study 2019](), [van Dyck et al. (NEJM, 2022)]()

Leqembi targets primarily patients with early-stage Alzheimer’s disease, but what about delaying the onset of dementia?

Hypertension: an opportunity for drug repurposing against dementia



45% of dementia risk attributable to **modifiable risk factors**.

For 5 out of 14 modifiable risk factors, **pharmaceutical interventions** are available:

1. Hypertension (2%)
2. High LDL cholesterol (7%)
3. Depression (3%)
4. Type 2 diabetes (2%)
5. Obesity (1%)

Hypertension

a. Affects 45% of the US adult population aged 18+
b. Associated with a 42% higher risk of dementia if untreated and 13% if treated

Sources: *Lennon et al. (JAMA Network Open, 2023)*, *Cholerton et al. (Diabetes Spectrum, 2016)*

Could certain antihypertensives have the added benefit of delaying the onset of dementia?

Neurology® Genetics

A peer-reviewed clinical and translational neurology open access journal

RESEARCH ARTICLE | August 29, 2022 |

Check for updates

Genetic Evidence for Protective Effects of Angiotensin-Converting Enzyme Against Alzheimer Disease But Not Other Neurodegenerative Diseases in European Populations

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Step 1
Mine genetic epidemiology studies to identify gene variants related to dementia risk

1. Co-localization analyses identified a gene variant for three traits (chr. 17, *rs4291*).

1. Directionality of the associations:

    a. Lower ACE expression, lower SBP
    b. Lower ACE, higher risk of AD
    c. No association btw predicted SBP and AD risk

Mendelian randomization of the ACE gene

Association	Directionality	Relation
ACE expression vs SBP	+	↓ ACE ~ ↓ SBP
ACE expression vs AD risk	-	↓ ACE ~ ↑ AD
Predicted SBP vs AD risk		

Step 1
Mine genetic epidemiology studies to identify gene variants related to dementia risk

1. Co-localization analyses identified a gene variant for three traits (chr. 17, *rs4291*).

2. Directionality of the associations points to a possibly ***direct***, rather than ***mediated***, link between ACE and AD.

Mendelian randomization of the ACE gene

Association	Directionality	Relation
ACE expression vs SBP	+	↓ ACE ~ ↓ SBP
ACE expression vs AD risk	-	↓ ACE ~ ↑ AD
Predicted SBP vs AD risk		

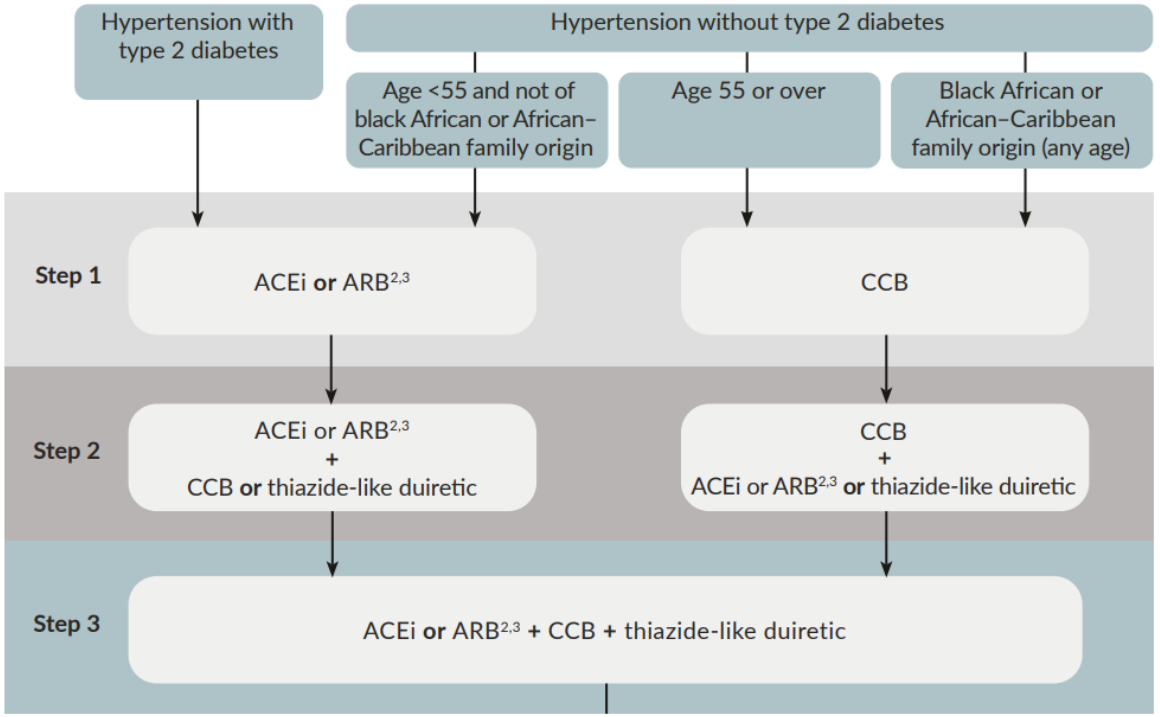
Variant of the ACE gene:
chr. 17, rs4291

Drug class mimicking the effect of this variant: ACE inhibitors

How to emulate a target trial, using medical records, to interrogate the hypothesis that ACEi initiation may have a detrimental effect on dementia?

Step 2
Derive a relevant, active comparator drug (class) from clinical guidelines

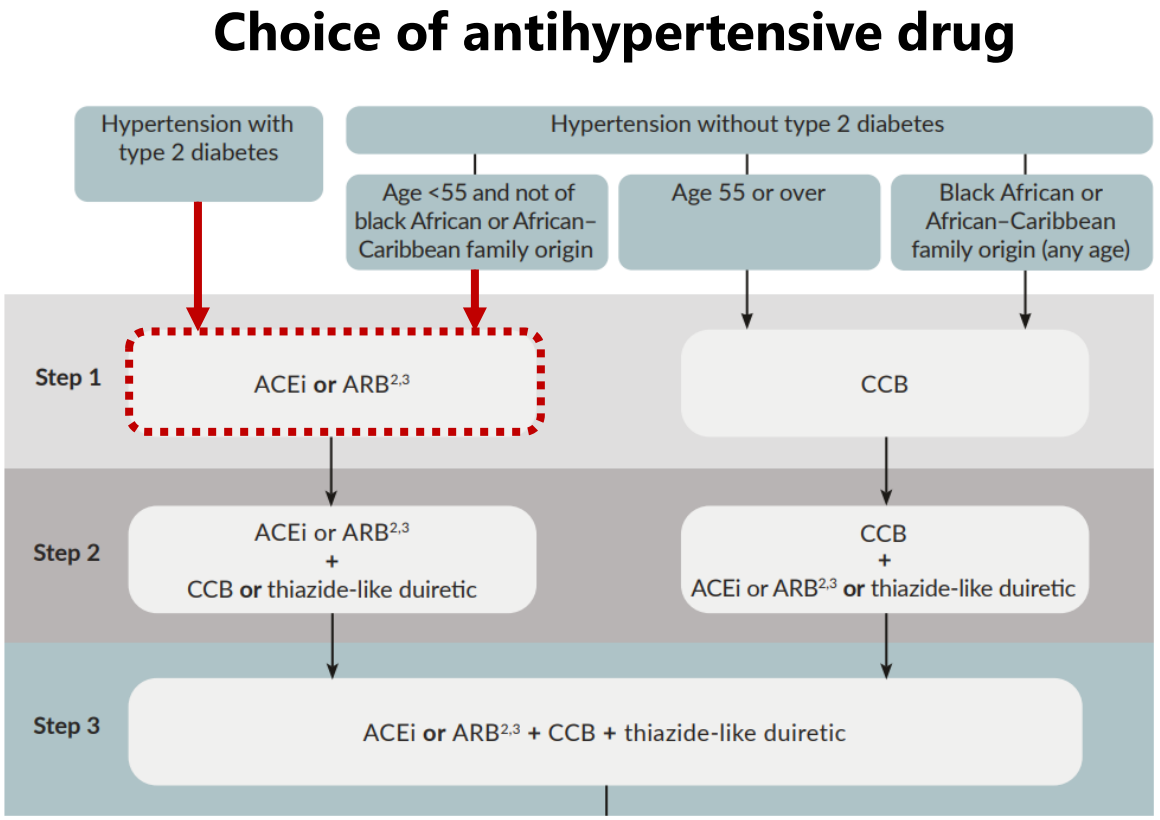
Choice of antihypertensive drug



Source: NICE hypertension guidelines (2019)

Step 2
Derive a relevant, active comparator drug (class) from clinical guidelines

Angiotensin receptor blockers (ARB) appear as a **natural active comparator** for ACE inhibitors.

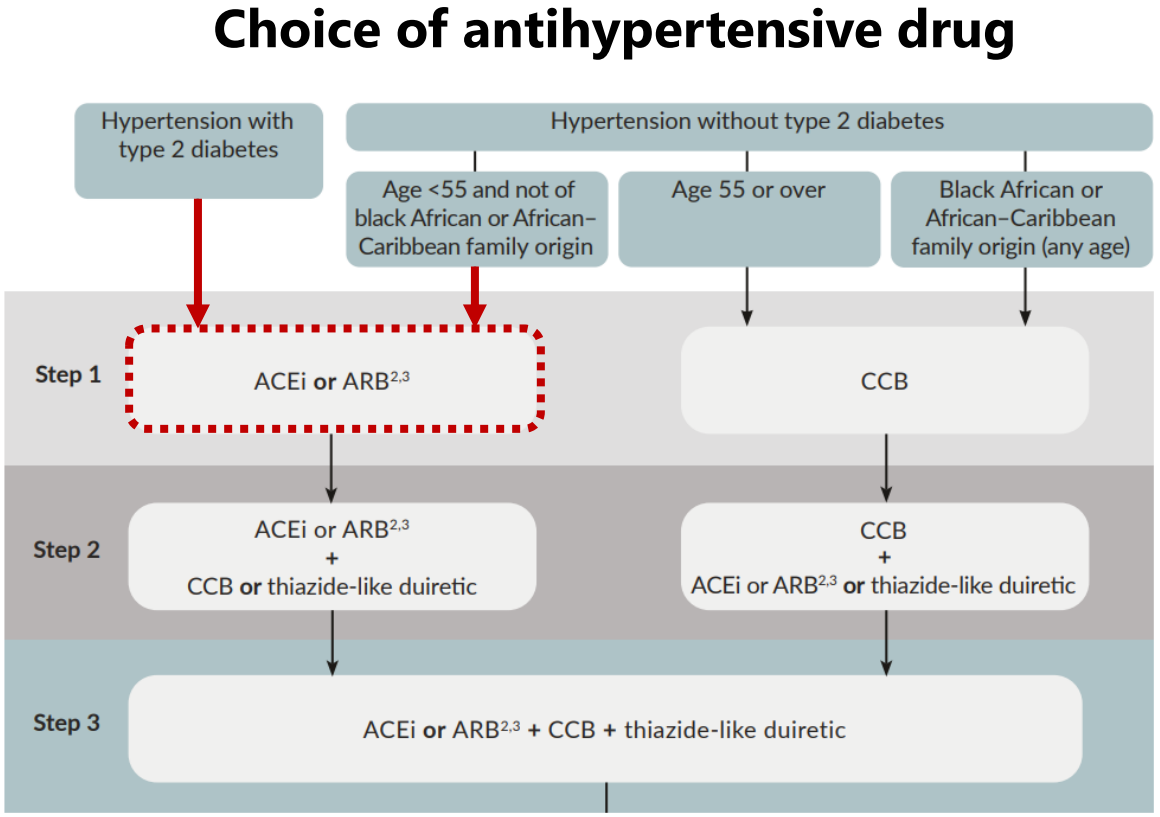


Source: NICE hypertension guidelines (2019)

Step 2
Derive a relevant, active comparator drug (class) from clinical guidelines

Angiotensin receptor blockers (ARB) appear as a **natural active comparator** for ACE inhibitors.

These two drug classes involve distinct mechanisms of action, making their comparison biologically relevant.



Source: NICE hypertension guidelines (2019)

Step 3
Emulate a target trial using EHR data

Causal question of interest

What is the effect of initiating an ACEi rather than an ARB on memory loss, mild cognitive impairment, or dementia among hypertensive adults aged 50 and over?

ACEi vs. ARB target trial specification & emulation

The target trial protocol comprises 7 components:

1. Eligibility criteria
2. Treatment strategies
3. Treatment assignment
4. Outcome definition
5. Follow-up definition
6. Causal contrasts
7. Statistical analysis

ACEi vs. ARB target trial specification & emulation

1. Eligibility criteria
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The hypothetical target trial includes
6 main inclusion/exclusion criteria:

1. Age 50 or over.
2. No prior outpatient prescription of any ACEi or ARB.
3. Prior diagnosis of hypertension.
4. No prior diagnosis of dementia in any setting.
5. No prior prescription of any dementia-related drugs in any setting.
6. Prior history of 1+ year within the EHR system.

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Initiation of 1 of the 2 following treatment strategies:

- Immediate treatment with an ACE inhibitor (ACEi)
- Immediate treatment with an angiotensin receptor blocker (ARB)

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Emulated randomization by balancing baseline confounders via overlap weighting:

- Sociodemographics: *age, sex, educational attainment, social vulnerability*
- Comorbidities: *prior history of type 2 diabetes, stroke, cardiovascular disease, cancer*
- Healthcare and temporal factors: *presence of primary care physician, time since enrollment in EHR system*

ACEi vs. ARB target trial specification & emulation

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Two mutually-exclusive, competing events

1. Incidence of memory loss, mild cognitive impairment, or dementia.
2. Death prior to such an event.

Outcome ascertainment

1. Diagnosis codes and drug prescriptions.
2. Death information internal to the healthcare system, supplemented by linkage to the national death index and state-level vital records.

ACEi vs. ARB target trial specification & emulation

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For each patient, the follow-up starts at treatment initiation (a.k.a. baseline or time 0) and **ends at the first of the following dates**:

1. Dementia onset
2. Death prior to dementia
3. Loss to follow-up
4. Administrative end of study

Five representative patient scenarios

Patient Number

#1

#2

#3

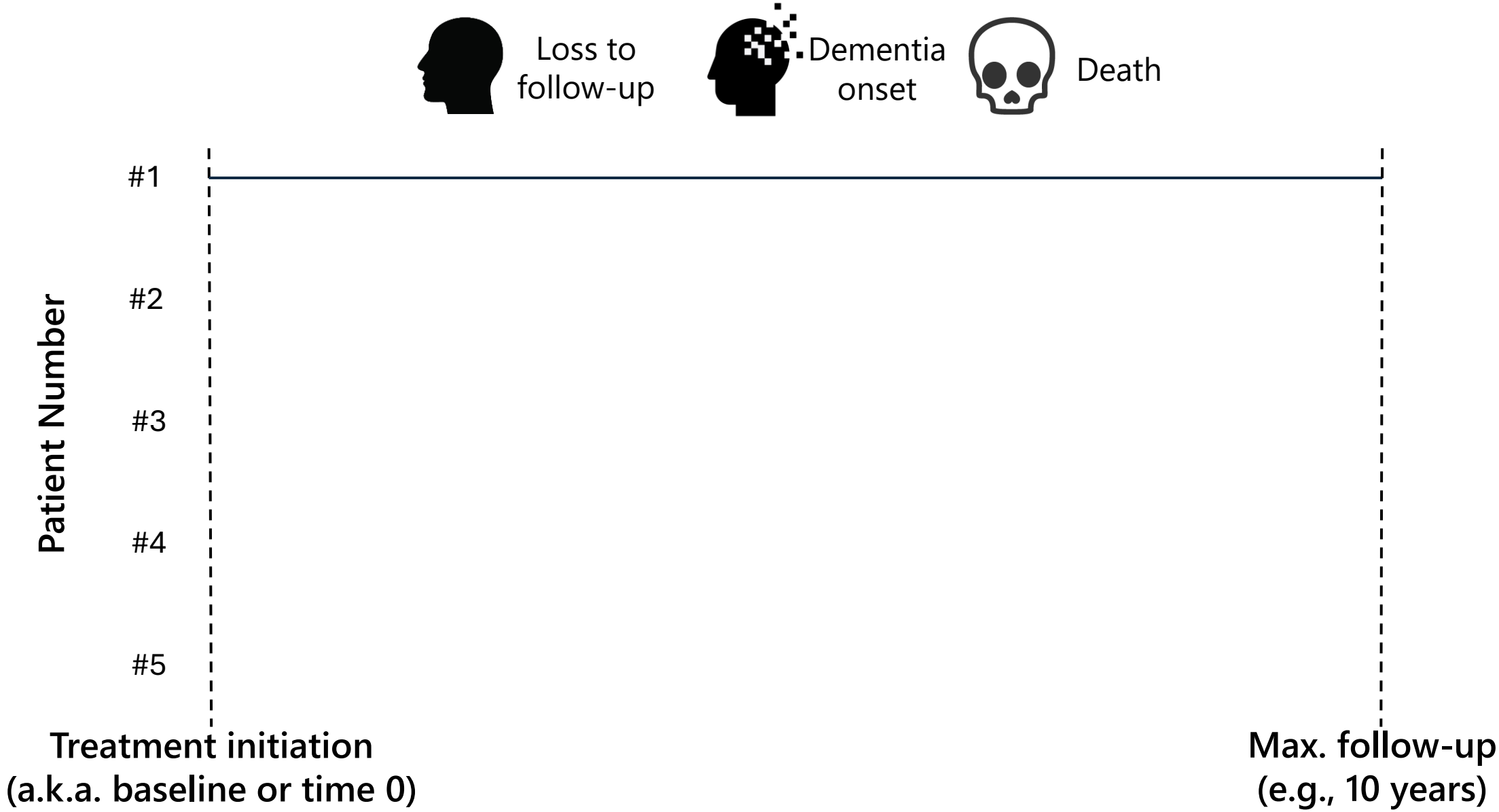
#4

#5

Treatment initiation (a.k.a. baseline or time 0)

Max. follow-up (e.g., 10 years)

Five representative patient scenarios



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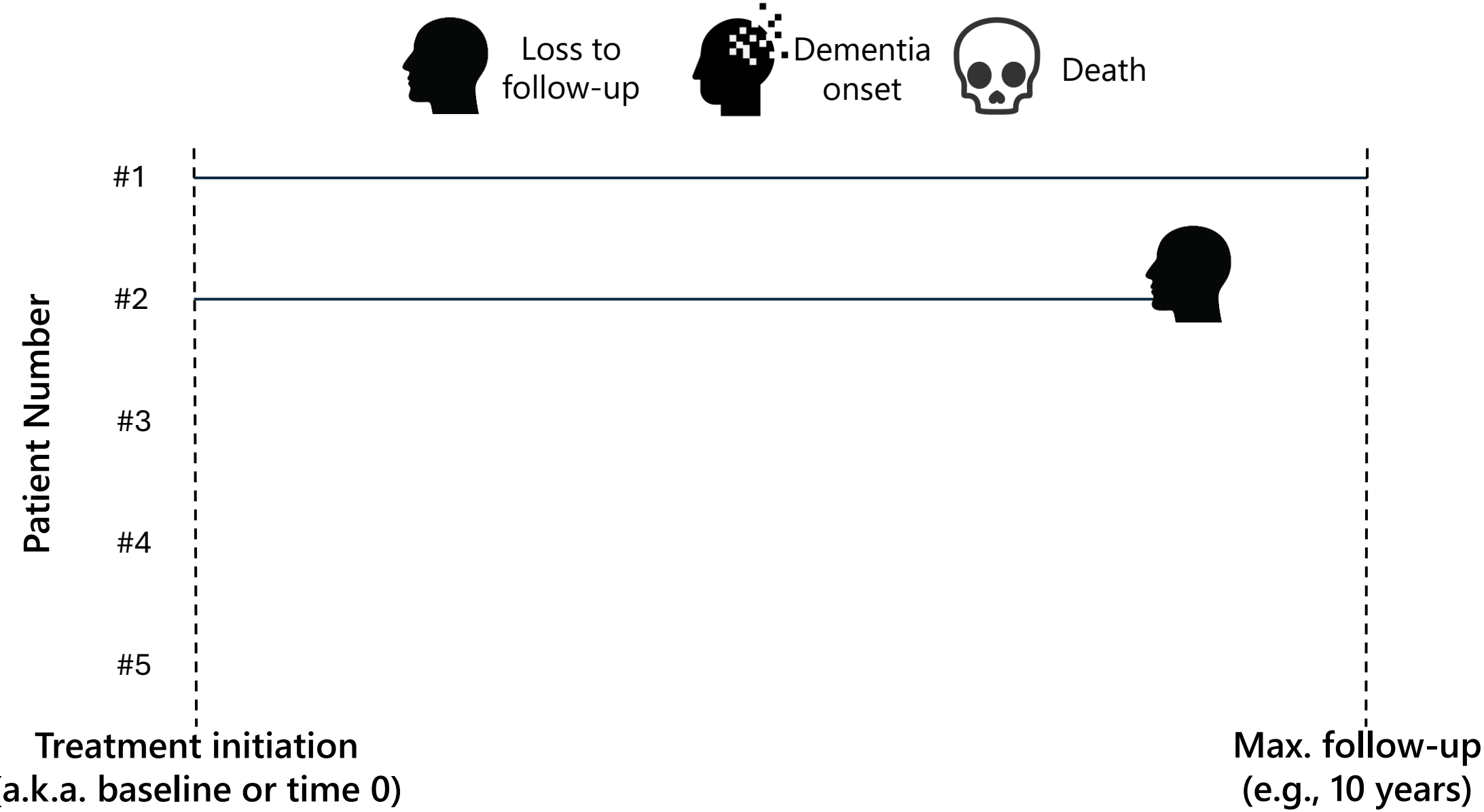

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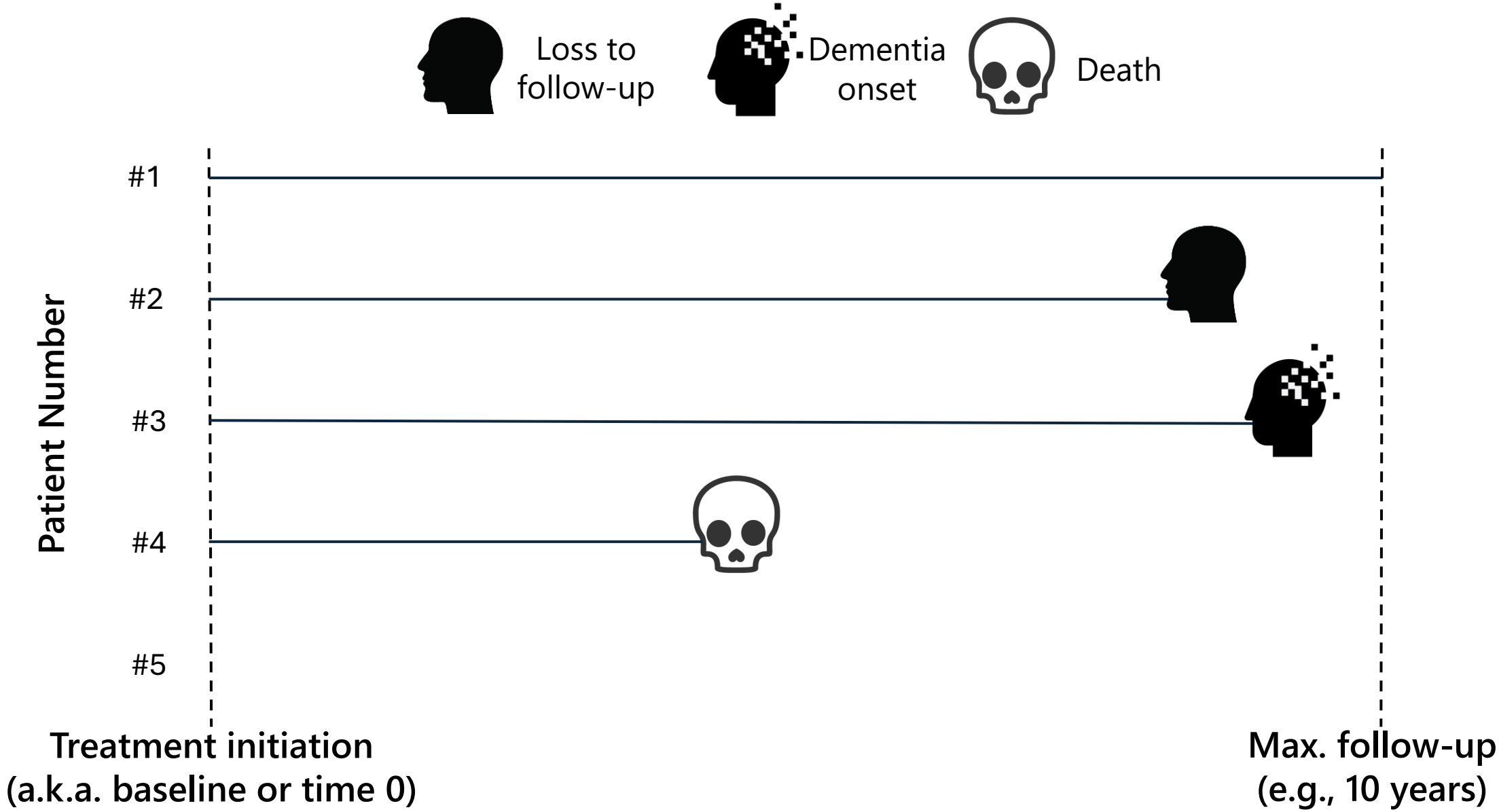

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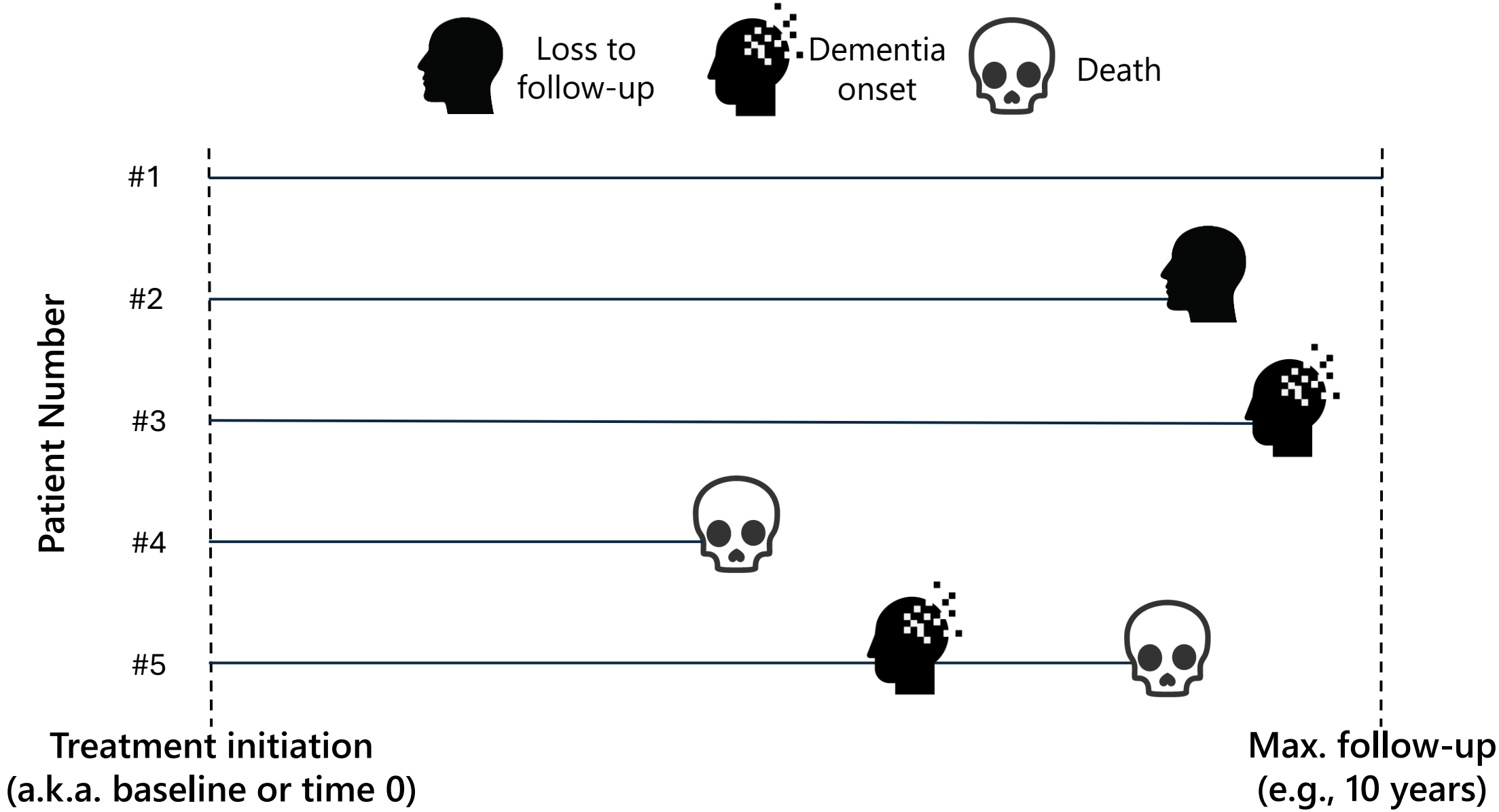

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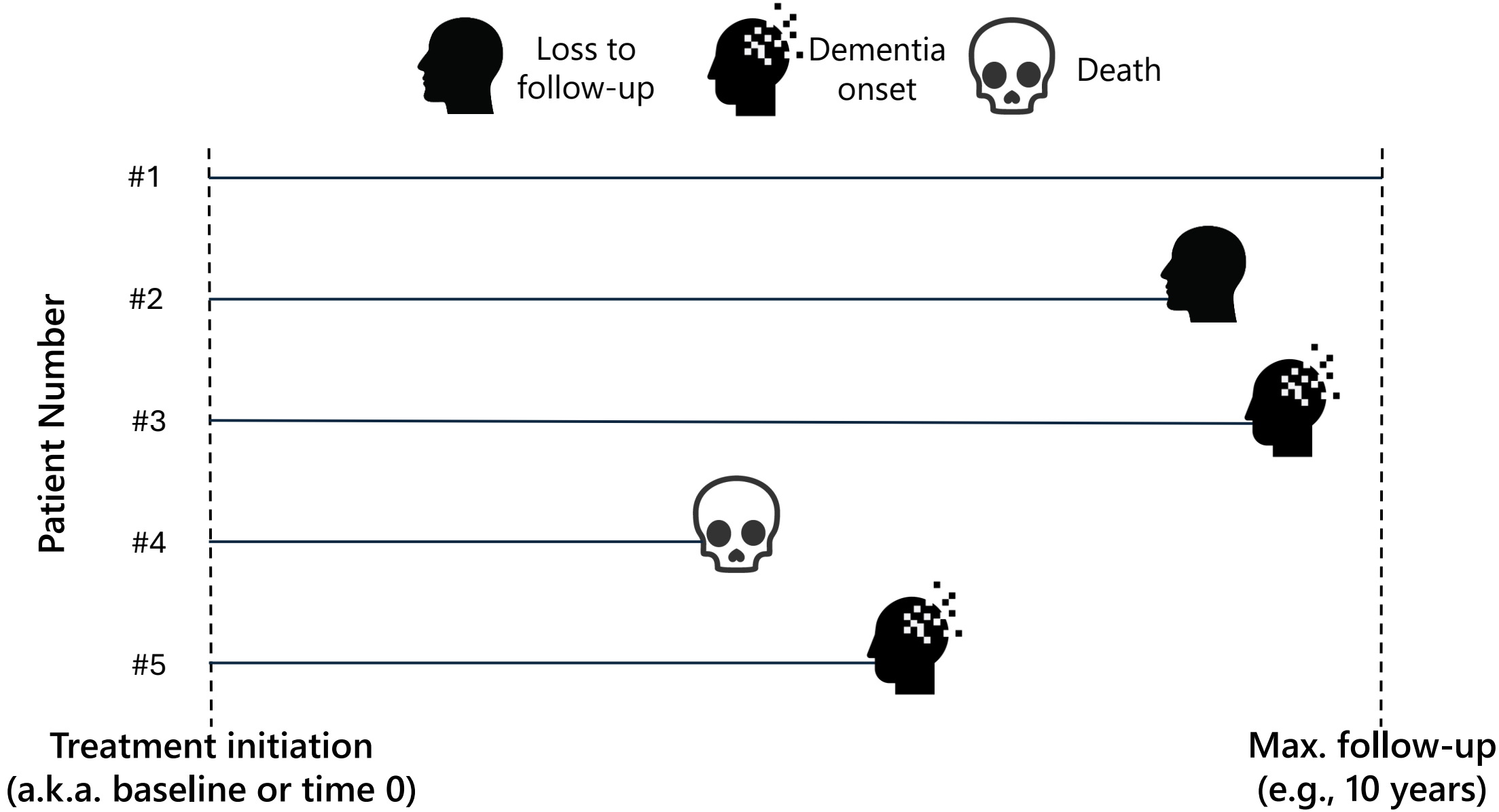
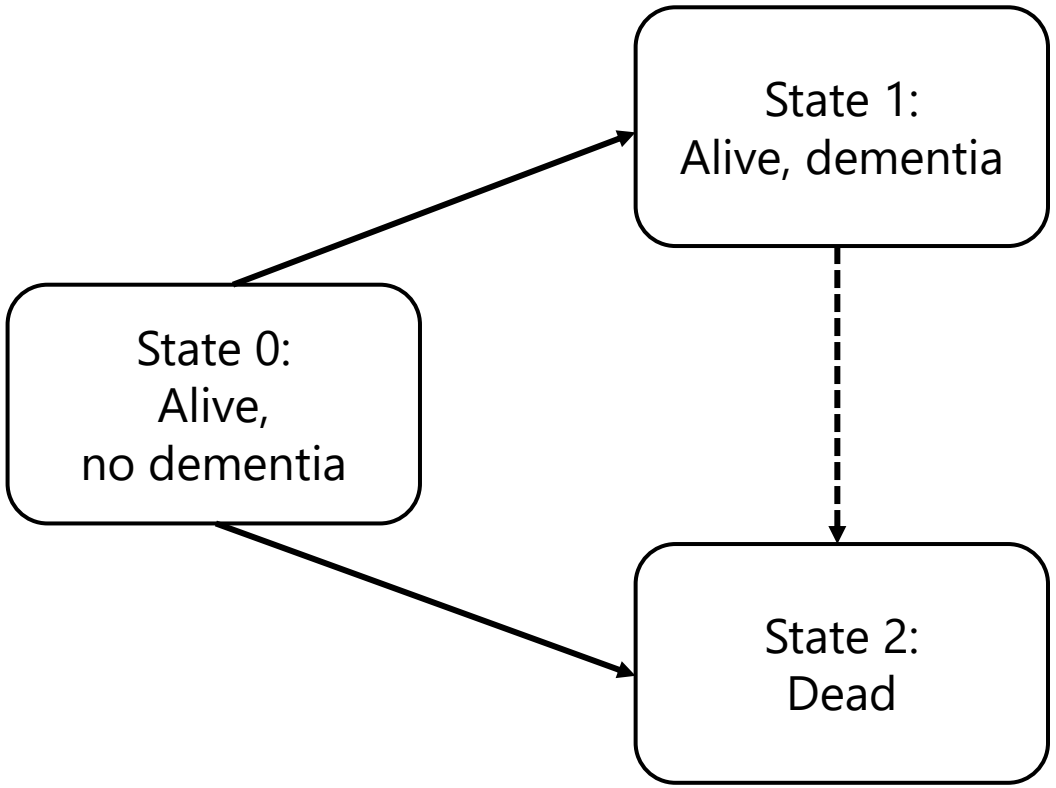


How to capture these different scenarios statistically?

Multi-state model representation

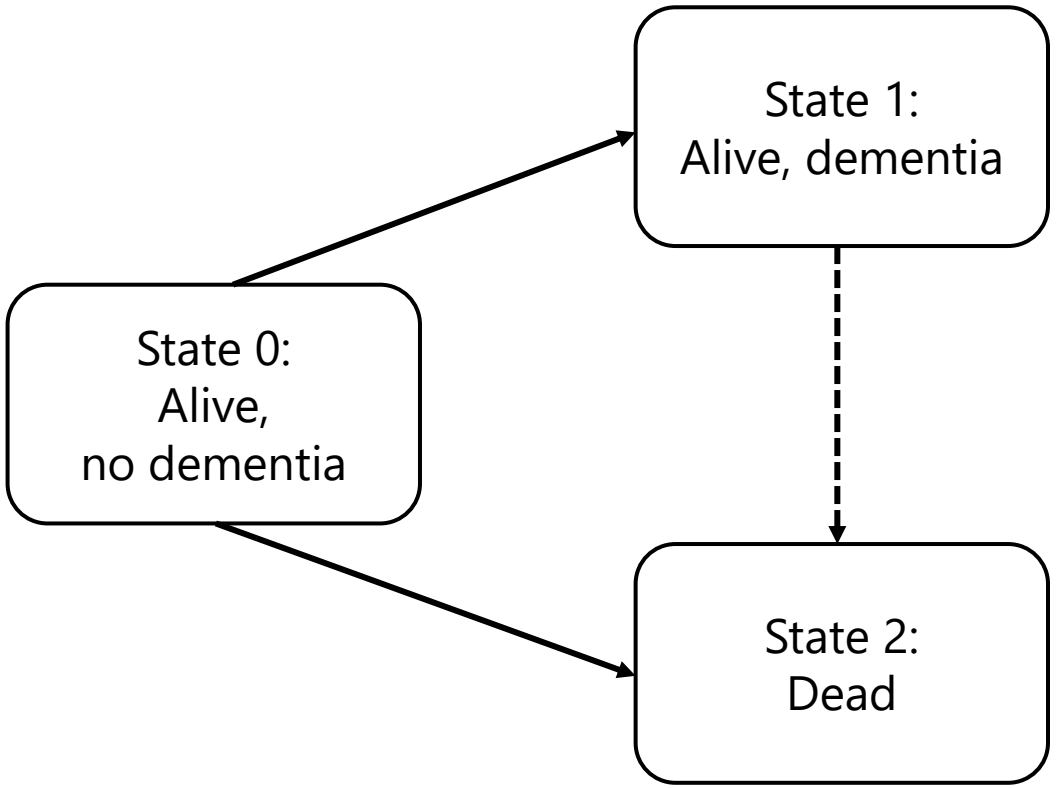


Illness-death model, with 3 states

At treatment initiation
All patients are in state 0.

From treatment initiation onwards
Patients can either go through state 1 before ultimately reaching state 2
or move directly to state 2.

Multi-state model representation



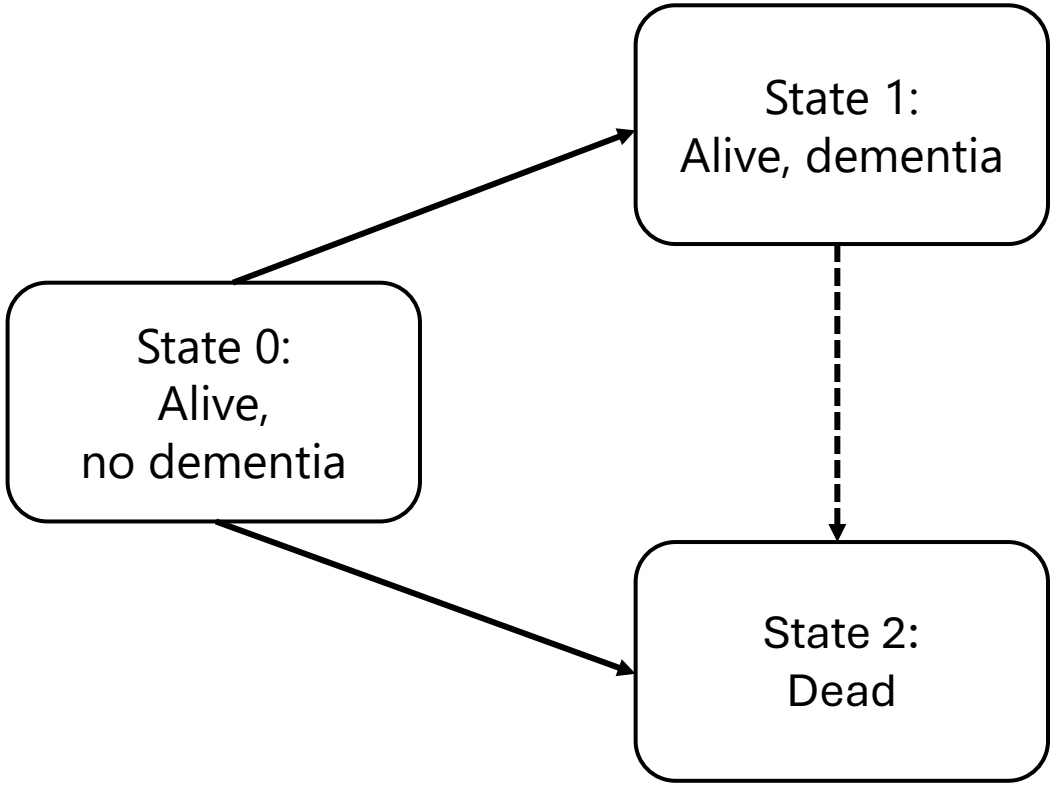
Illness-death model, with 3 states

At treatment initiation

1. Which path the patient will take is unknown.

2. Two latent time-to-event variables can be defined.

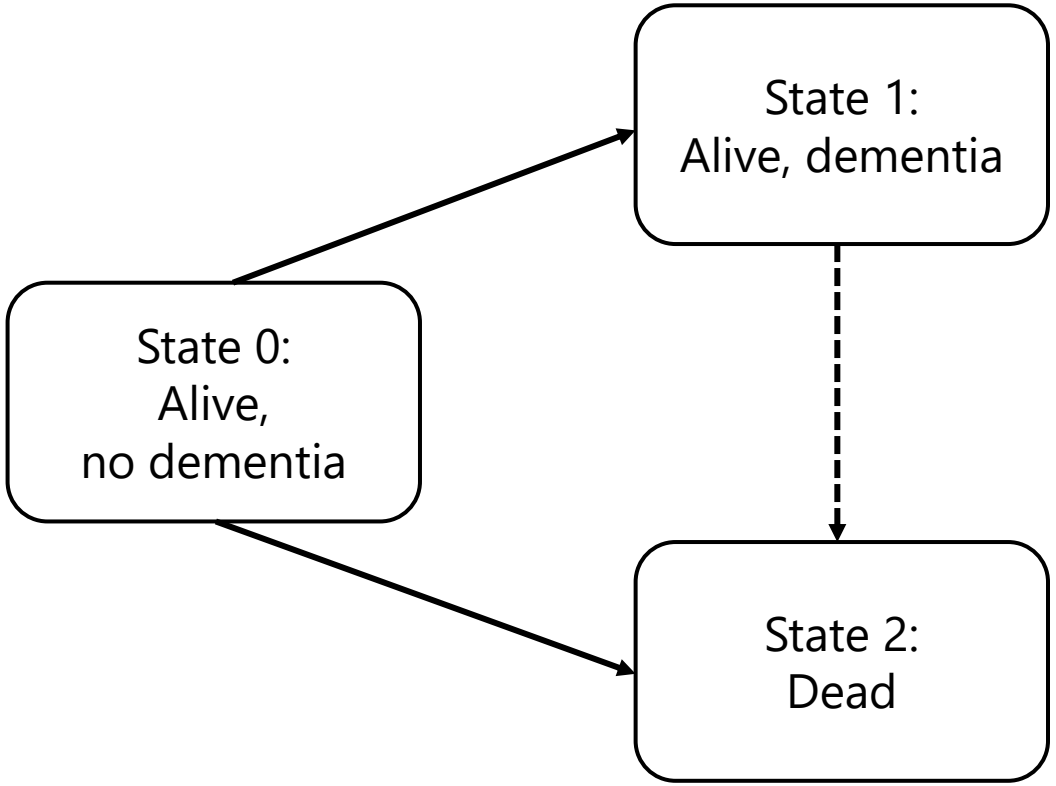
Multi-state model representation



Illness-death model, with 3 states

Random variable $U_{0\to1}$
Time from treatment initiation until reaching state 1

Multi-state model representation

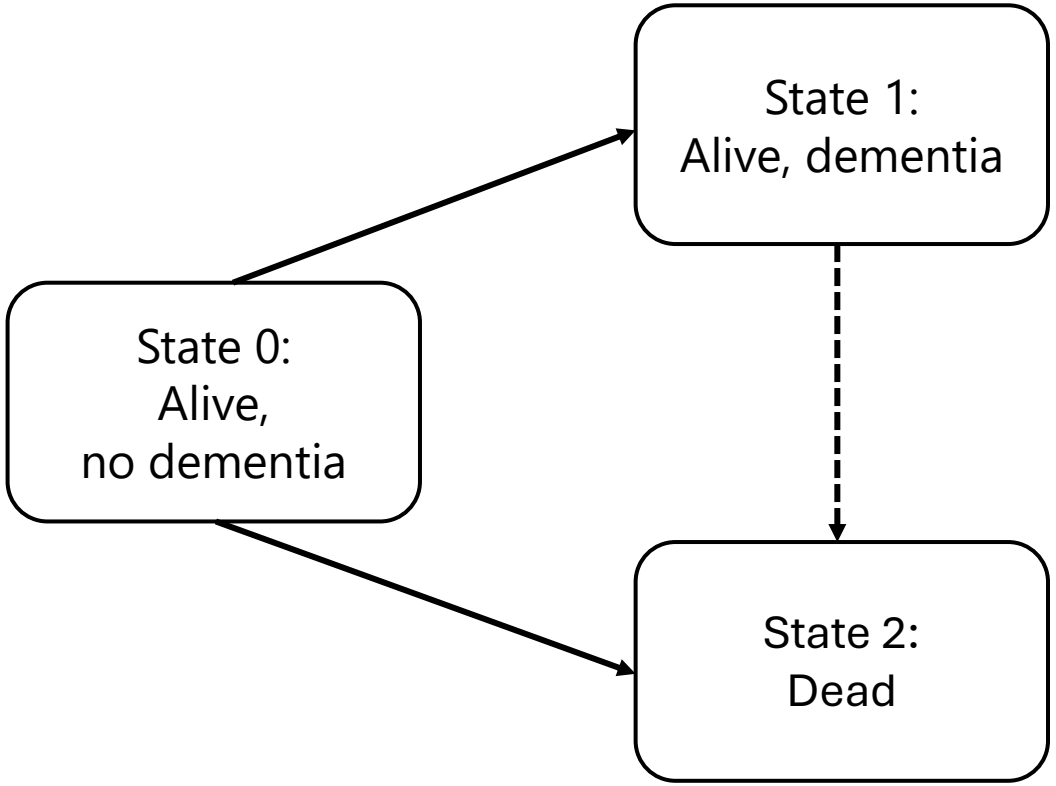


Illness-death model, with 3 states

Random variable $U_{0\to1}$
Time from treatment initiation until reaching state 1

Random variable $U_{0\to2}$
Time from treatment initiation until reaching state 2 without going through state 1

Multi-state model representation



Illness-death model, with 3 states

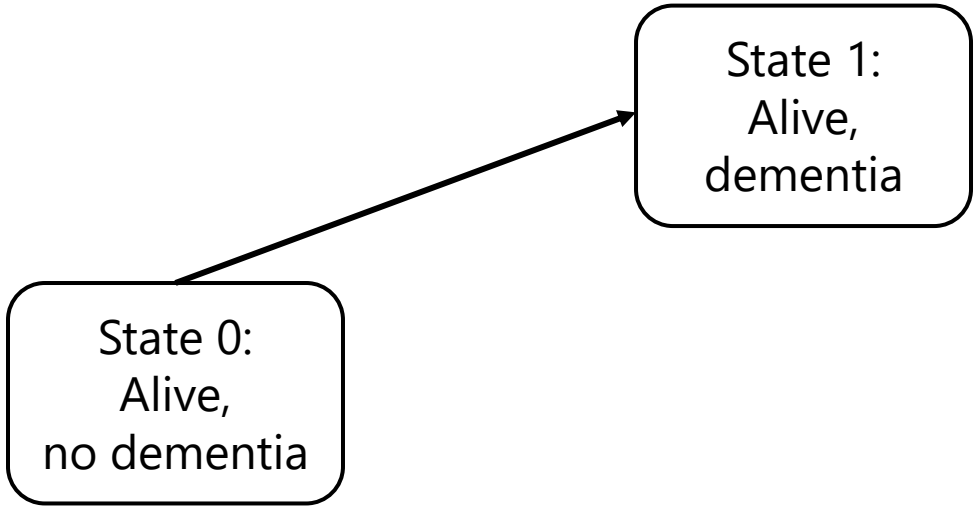
Ultimately, only the minimum of the two time-to-event variables will ever be observed:

$$\boldsymbol{U = \min(U_{0\to 1}, U_{0\to 2})}$$

The corresponding integer-valued variable $\boldsymbol{F \in \{1, 2\}}$ indicates the type of event that occurs first.

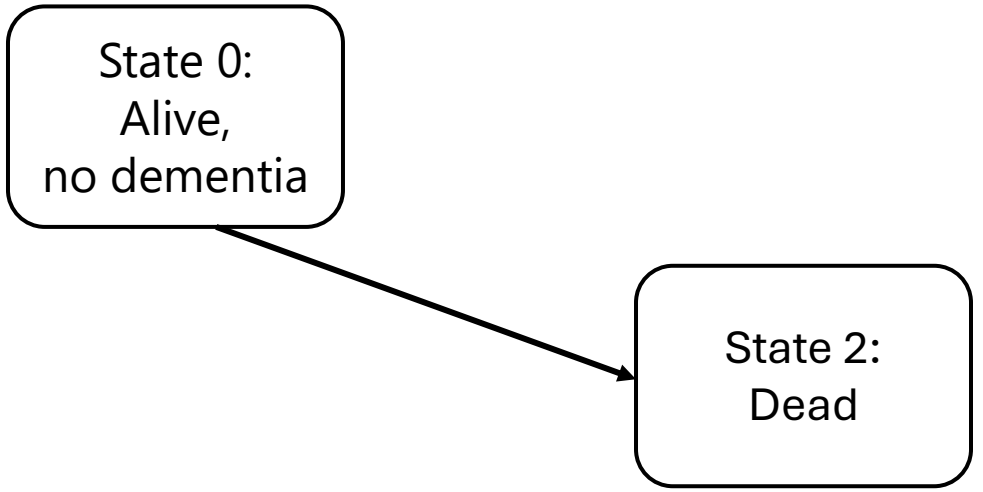
What is the nature of observations made in the EHR?

Observed transitions

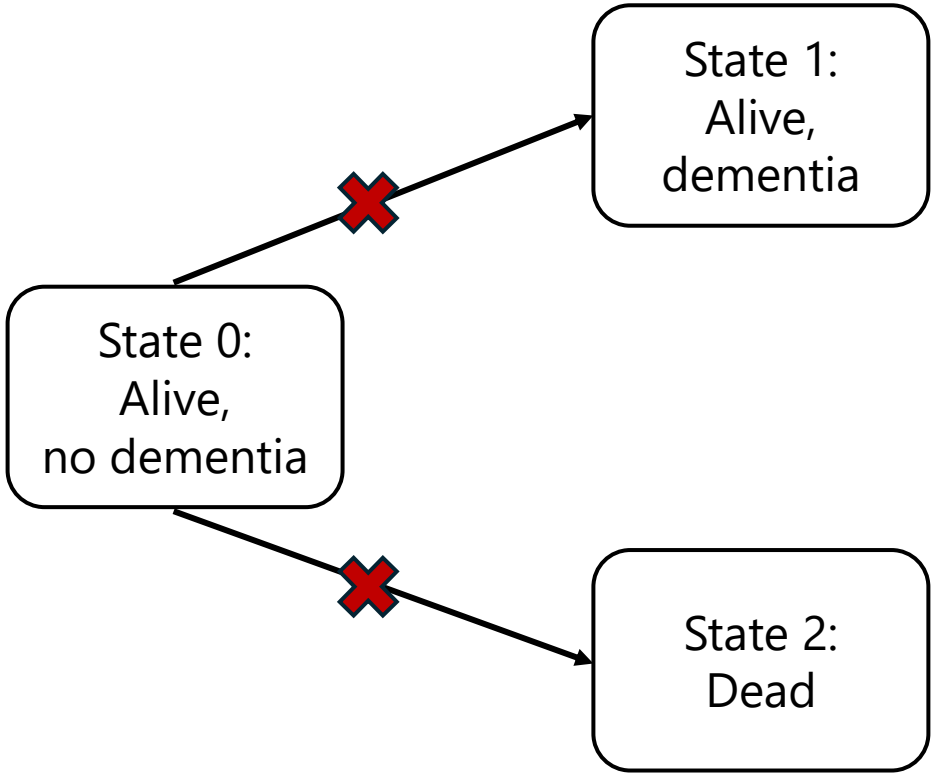


$$\boldsymbol{U = U_{0\to1}, F = 1}$$

$$\boldsymbol{U = U_{0\to2}, F = 2}$$



No observed transition



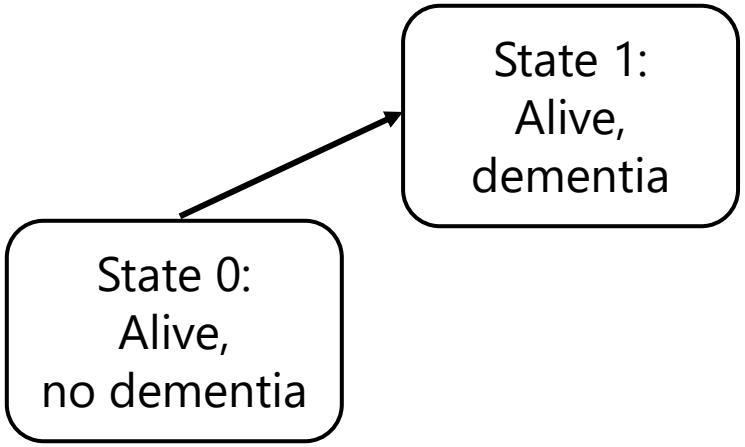
The patient remains in state 0 during follow-up. This scenario corresponds to **right-censoring**.

If the random variable $\boldsymbol{C}$ represents the censoring time, then the follow-up time $\boldsymbol{T}$ is defined by:

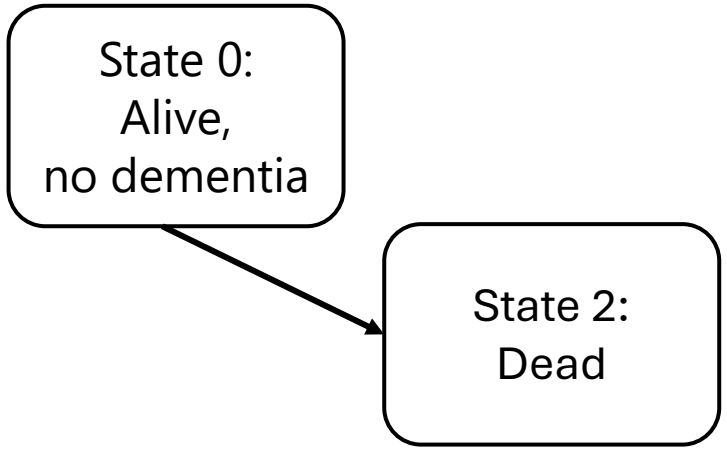
$$\boldsymbol{T = \min(U, C) = \min(U_{0\to1}, U_{0\to2}, C)}$$

The integer-valued variable $\boldsymbol{E \in \{0, 1, 2\}}$ maps each patient to the corresponding **scenario** (0 for no transition).

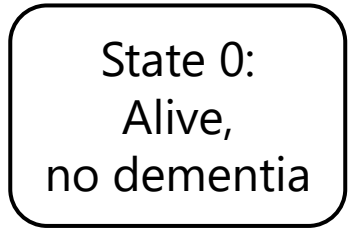
Summary of notations



$$\boldsymbol{T = U = U_{0\to 1}}$$
$$\boldsymbol{E = F = 1}$$



$$\boldsymbol{T = U = U_{0\to 2}}$$
$$\boldsymbol{E = F = 2}$$



$$\boldsymbol{T = C}$$
$$\boldsymbol{E = 0}$$

All quantities considered so far are based on observed data!

Definition of counterfactual worlds

To address the causal question, we define **two counterfactual, single worlds** denoted by $\boldsymbol{a}$:

$$\boldsymbol{a = 1}$$

a world in which all patients had received an initial prescription of an ACEi

$$\boldsymbol{a = 0}$$

a world in which all patients had received an initial prescription of an ARB

Definition of potential outcomes

Counterfactual outcomes $\boldsymbol{Y(a)}$ are defined accordingly.

$$\boldsymbol{Y(a=1)}$$

outcome had the patient received an initial prescription of an ACEi

$$\boldsymbol{Y(a=0)}$$

outcome had the patient received an initial prescription of an ARB

What are the potential outcomes of interest in our setting?

Potential outcomes under no right-censoring

Setting 1: Competing risks, but no right-censoring

Potential outcomes are pairs $(\boldsymbol{U^a}, \boldsymbol{F^a})$ where:

- The positive real-valued variable $\boldsymbol{U^a}$ denotes the time to the first of two mutually-exclusive, competing events in counterfactual world $\boldsymbol{a}$.
- The integer-valued variable $\boldsymbol{F^a} \in \{\boldsymbol{1}, \boldsymbol{2}\}$ indicates the type of event that occurs first in counterfactual world $\boldsymbol{a}$.

Potential outcomes under right-censoring

Setting 2: Competing risks and right-censoring

Potential censoring times need to be accounted for.

Potential outcomes are pairs $(\boldsymbol{T^a}, \boldsymbol{E^a})$ where:

- The positive real-valued variable $\boldsymbol{T^a = min(U^a, C^a)}$ denotes the follow-up time in counterfactual world $\boldsymbol{a}$.
- The integer-valued variable $\boldsymbol{E^a} \in \{\mathbf{0}, \mathbf{1}, \mathbf{2}\}$ indicates the scenario corresponding to the end of follow-up in counterfactual world $\boldsymbol{a}$.

ACEi vs. ARB target trial specification & emulation

1. Eligibility criteria
2. Treatment strategies
3. Treatment assignment
4. Outcome definition
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6. Causal contrasts
7. Statistical analysis

The causal contrast is defined based on the single-world ($a = 0$ vs. $a = 1$) causal quantities of interest, i.e., the **cumulative risk R** of experiencing dementia onset ($k = 1$) or dying before ($k = 2$).

$$R^a(t,k) = P(T^a \leq t, E^a = k)$$
$$= E\left[\int_0^t S^a(s) h_k^a(s) ds\right]$$

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$$R^a(t,k) = P(T^a \leq t, E^a = k)$$
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Survival in single-world a at time s or probability of being alive and not having dementia by that time

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$$R^a(t,k) = P(T^a \le t, E^a = k)$$
$$= E\left[\int_0^t S^a(s)\boldsymbol{h_k^a(s)}ds\right]$$

Cause-specific hazard in single-world $\boldsymbol{a}$
of experiencing event $\boldsymbol{k}$ at time $\boldsymbol{s}$

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For each competing event $\boldsymbol{k}$, the causal contrast is defined as the **difference in risk**, denoted by $\boldsymbol{RD}$, between the two single-worlds ($a = 0$ vs. $a = 1$).

$$t \mapsto \boldsymbol{RD}(t, \boldsymbol{k}) = R^{a=1}(t, \boldsymbol{k}) - R^{a=0}(t, \boldsymbol{k})$$

We chose risk differences as the causal contrasts to facilitate clinical interpretability.

In observational data, the treatment and control arms are often not balanced.

How to handle this statistically to estimate the effects of treatment on competing risks?

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    a. Assumptions
    b. Choice of weights
    c. Estimation

H1: Conditional exchangeability

H2: Positivity

H3: Conditionally independent censoring

H4: Stable Unit Treatment Value Assumption (SUTVA)

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H1: Conditional exchangeability
The treatment assignment A is assumed conditionally independent of potential outcomes $(U^{a=0}, U^{a=1})$, given baseline covariates X.

$$A \perp (U^{a=0}, U^{a=1}) \mid X$$

Similarly, A is assumed conditionally independent of potential censoring times $(C^{a=0}, C^{a=1})$, given X.

$$A \perp (C^{a=0}, C^{a=1}) \mid X$$

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H2: Positivity

For any set of covariates $X = x$ present in the population, there is a nonzero probability of being assigned to any arm a.

$$0 < P(A = a \mid X = x) < 1$$

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Use of overlap weights to emulate randomization

Given a set of covariates $X = x$, the corresponding overlap weight $\boldsymbol{w(x)}$ is defined as follows:

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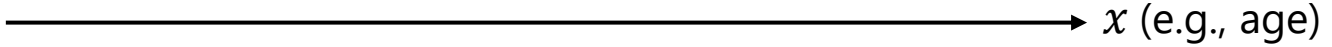

ACEi vs. ARB target trial specification & emulation

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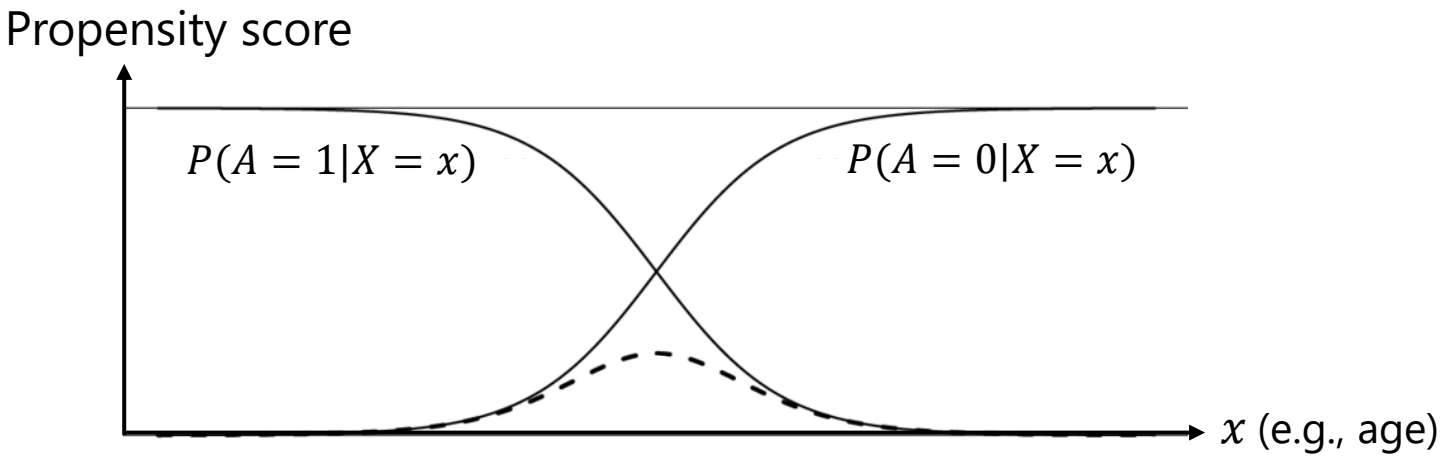

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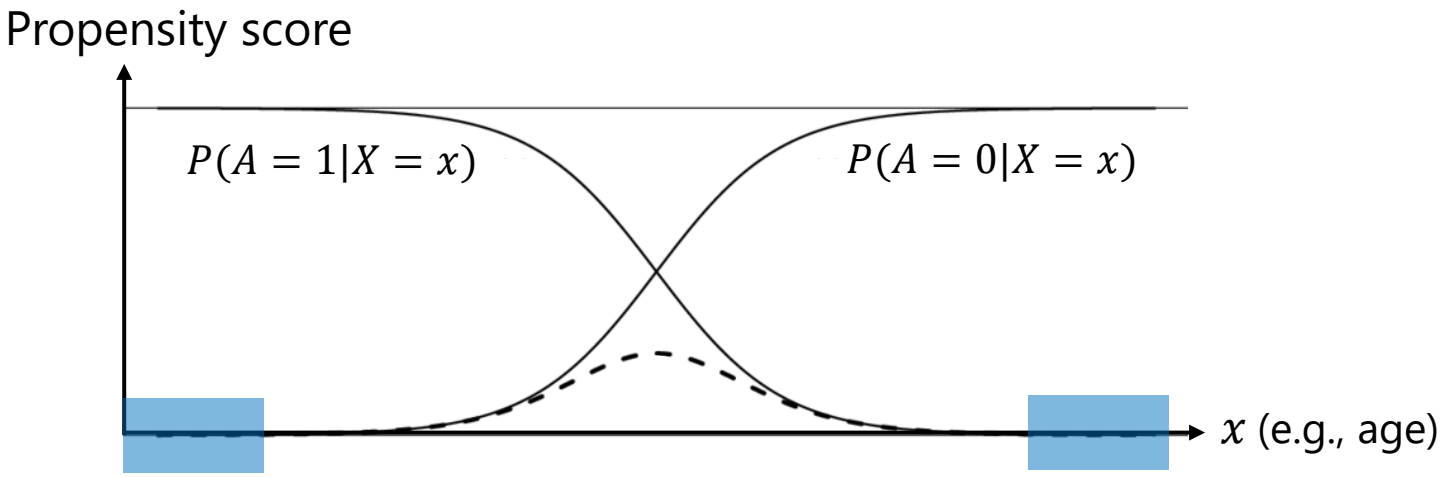

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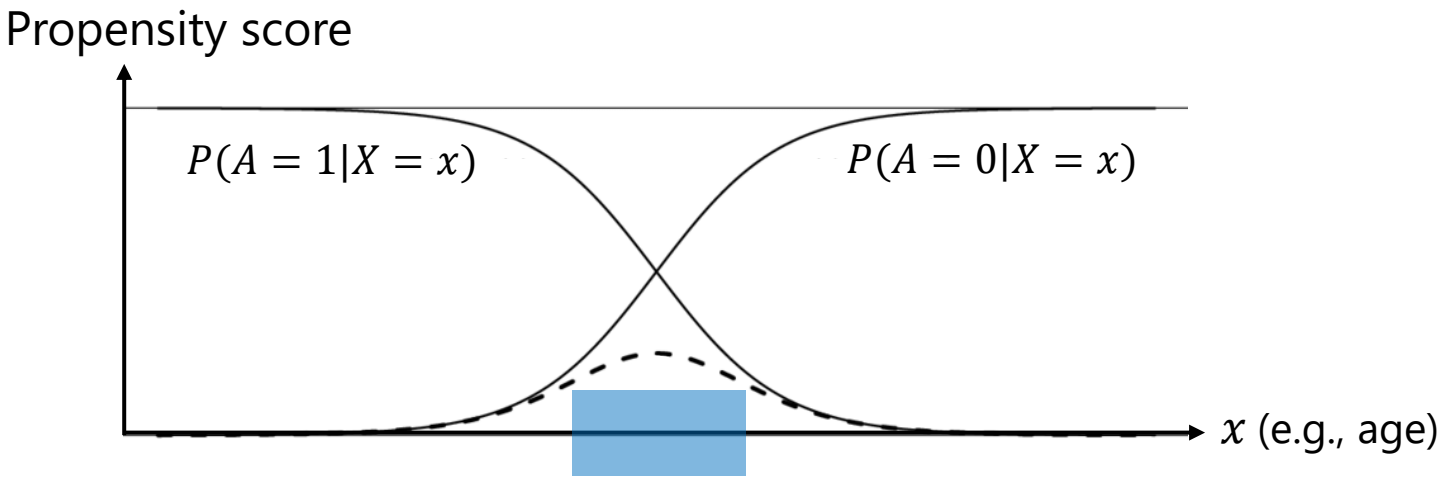

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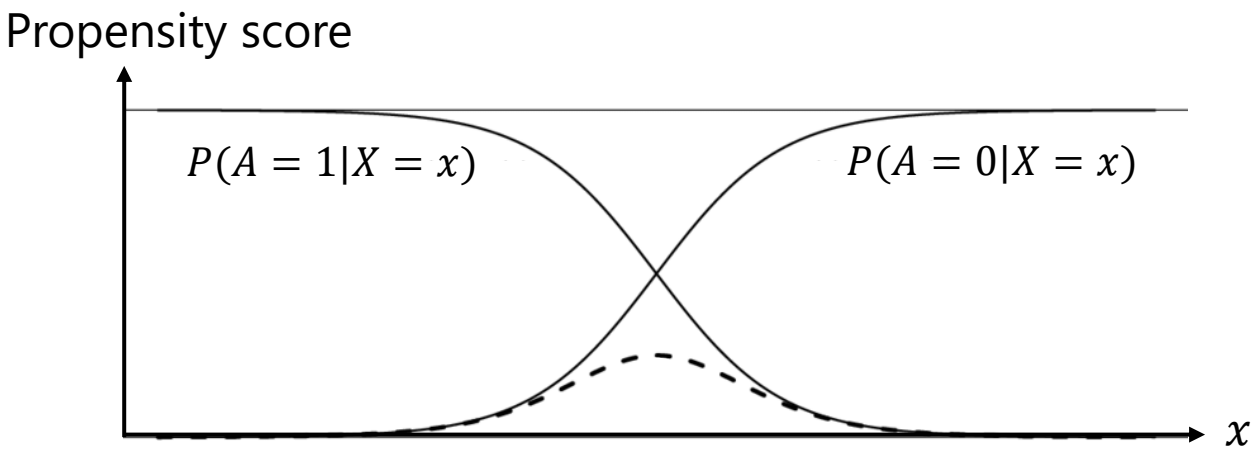
Use of overlap weights to emulate randomization

Given a set of covariates $X = x$, the corresponding overlap weight $\boldsymbol{w(x)}$ is defined as follows:

$$\boldsymbol{w(x)} = AP(A = 0|X = x) + (1 - A)P(A = 1|X = x)$$



Why using overlap weights?

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Statistical advantages

1. Overlap weights are bounded.

2. If propensity scores are estimated by maximum likelihood with a logistic regression, then equality of covariate means is achieved.

3. The nonparametric estimator for the ATO has minimum variance among all WATE estimators with balancing weights.

ATO: average treatment effect in the overlap population,
WATE: weighted average treatment effect

Sources: Li, Morgan, and Zaslavsky (JASA, 2017) & Li, Thomas, and Li (AJE, 2018)

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Clinical relevance

1. The overlap-weighted population corresponds to patients in clinical equipoise, whose covariates could appear with high probability in any arm.

2. The ATO may be more generalizable than other effect measures.

ATO: average treatment effect in the overlap population

Source: Thomas, Li, and Pencina (JAMA, 2020)

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The statistical estimation procedure involves **4 steps**.

In what follows, we assume proportional hazards, but it can be relaxed.

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Step 4: Estimator of the **cause- or event-specific** risk difference function $\widehat{RD_k}$ for $\boldsymbol{k} \in \{1,2\}$

What did we learn from applying this target trial emulation approach to real-world EHR data?

Data overview

1. Data source

Research Patient Data Registry at an academic healthcare system on the US East Coast.

Data overview

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Mass General Brigham

Research Patient Data Registry at an academic healthcare system on the US East Coast.

2. Study period

Outpatient prescription orders made between January 1, 2010, and January 31, 2020.

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Research Patient Data Registry at an academic healthcare system on the US East Coast.

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Outpatient prescription orders made between January 1, 2010, and January 31, 2020.

3. Cohort size and arm split

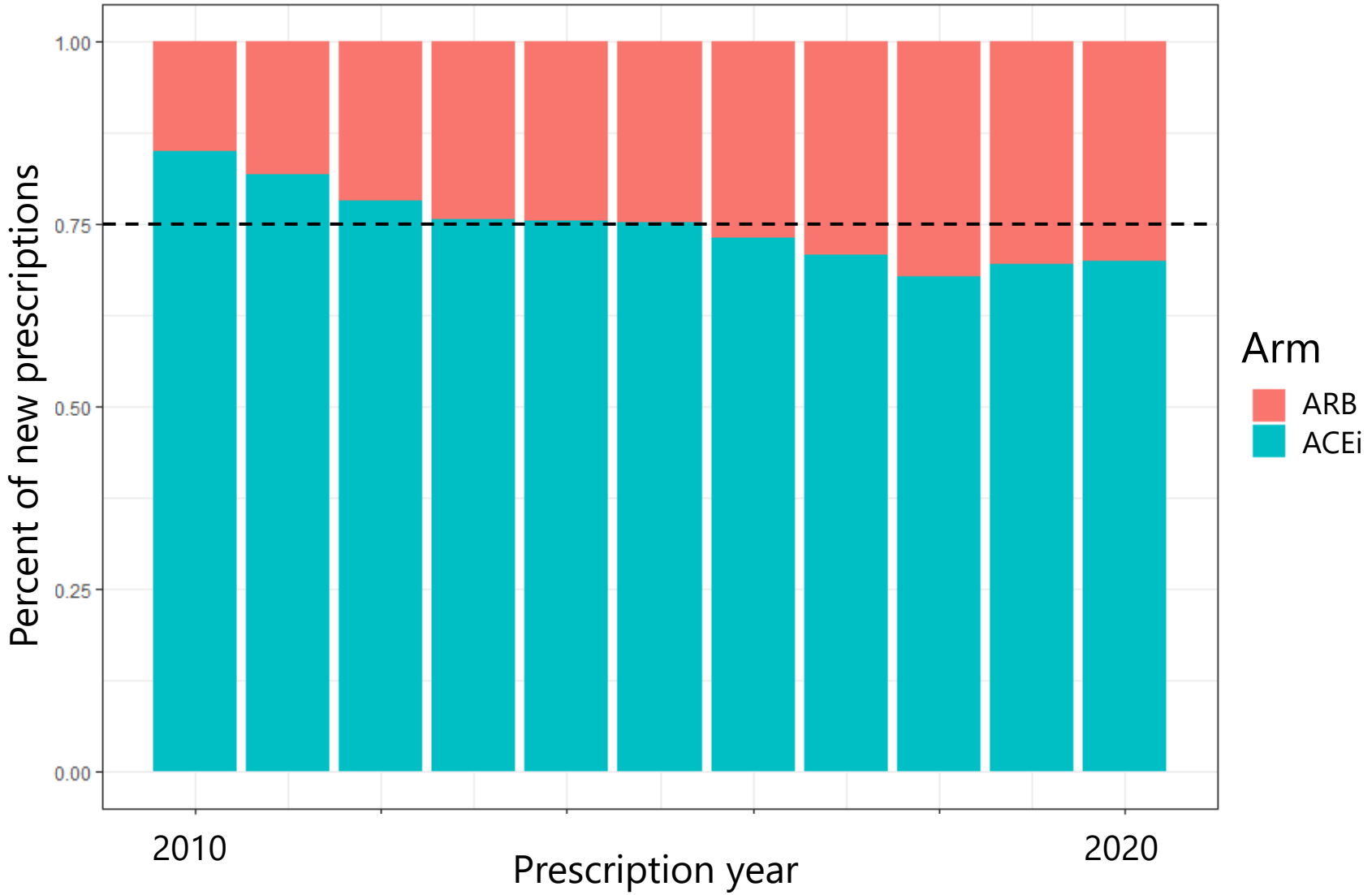
25,507 hypertensive patients aged 50+

Uneven split between original arms

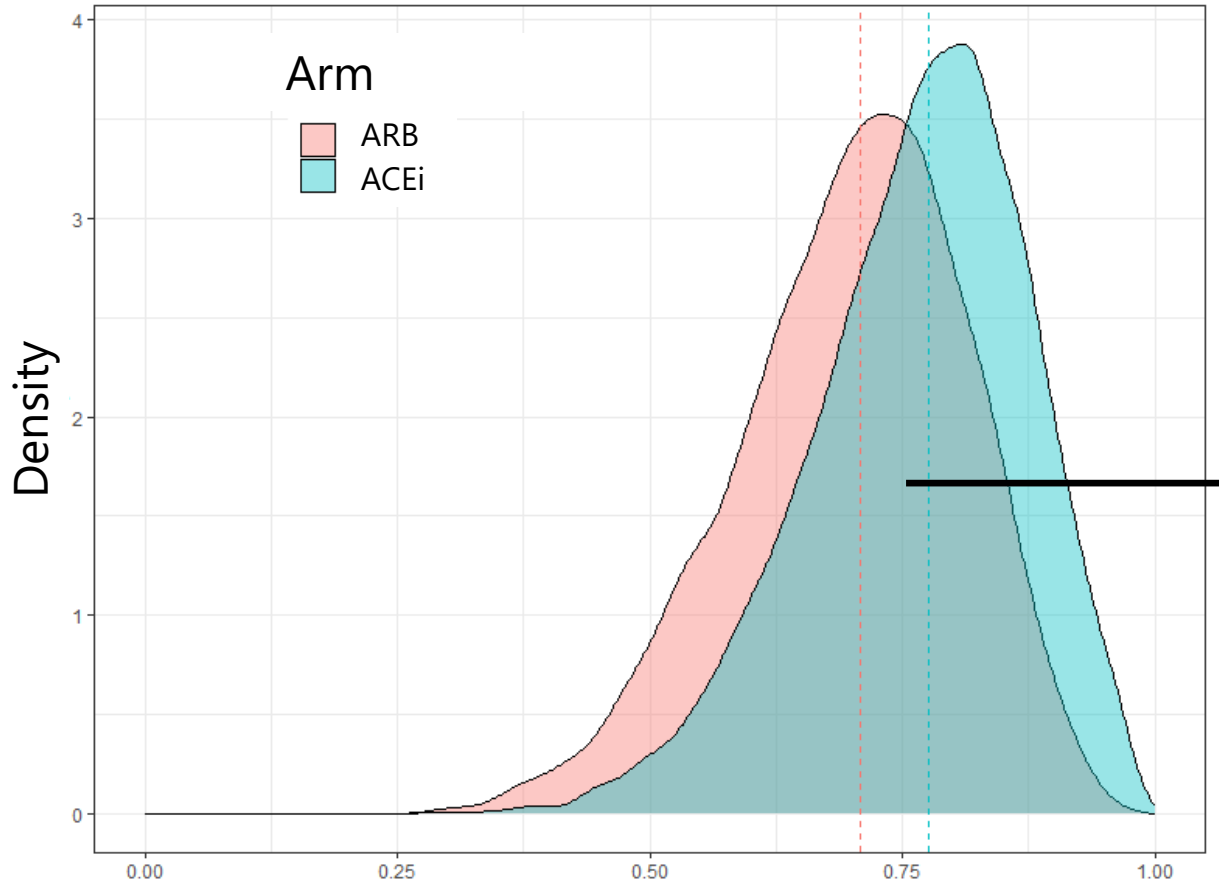
ARB initiators
25.2%

ACEi initiators
74.8%

Temporal patterns of ACEi/ARB drug prescriptions

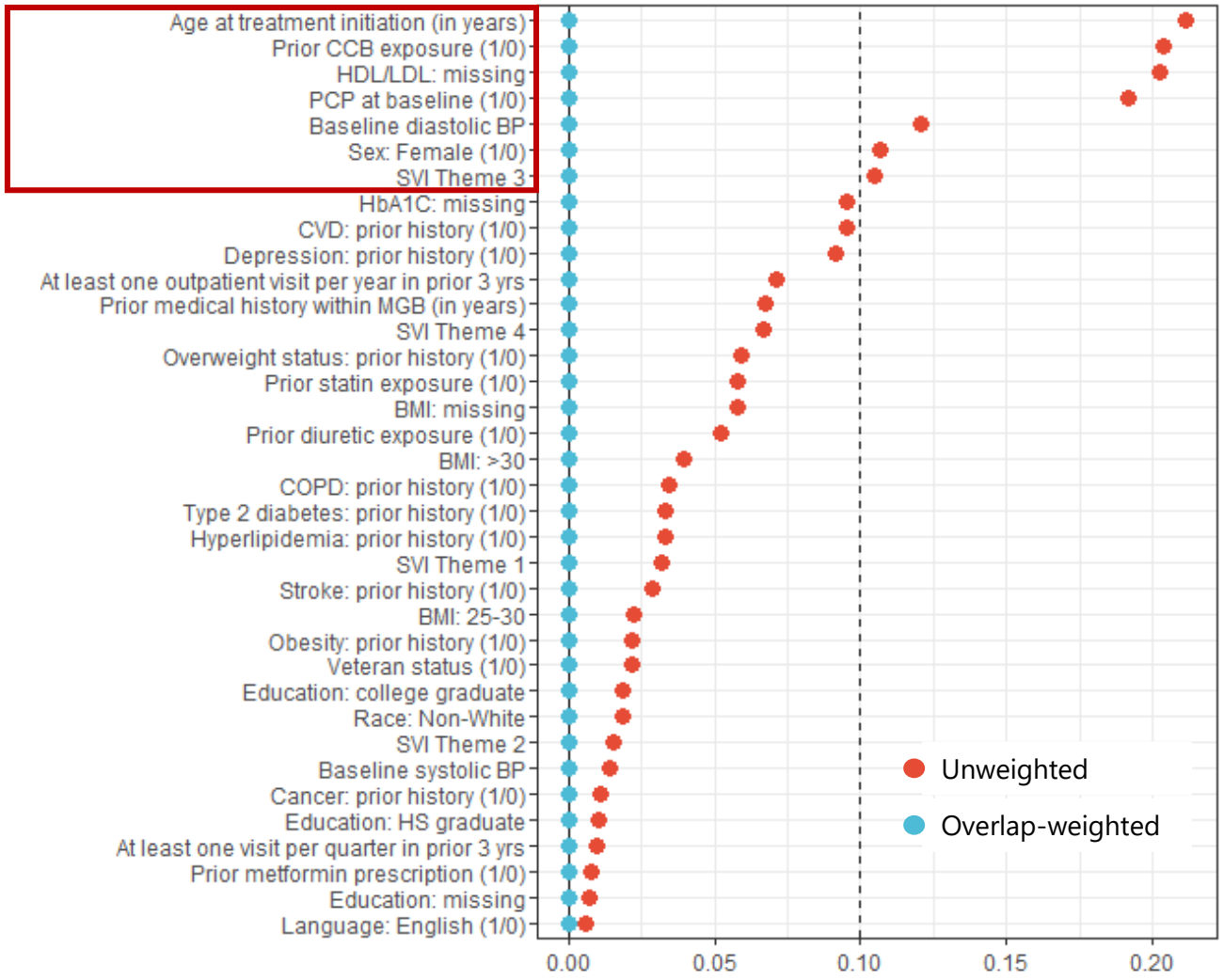


Assessment of overlap between arms



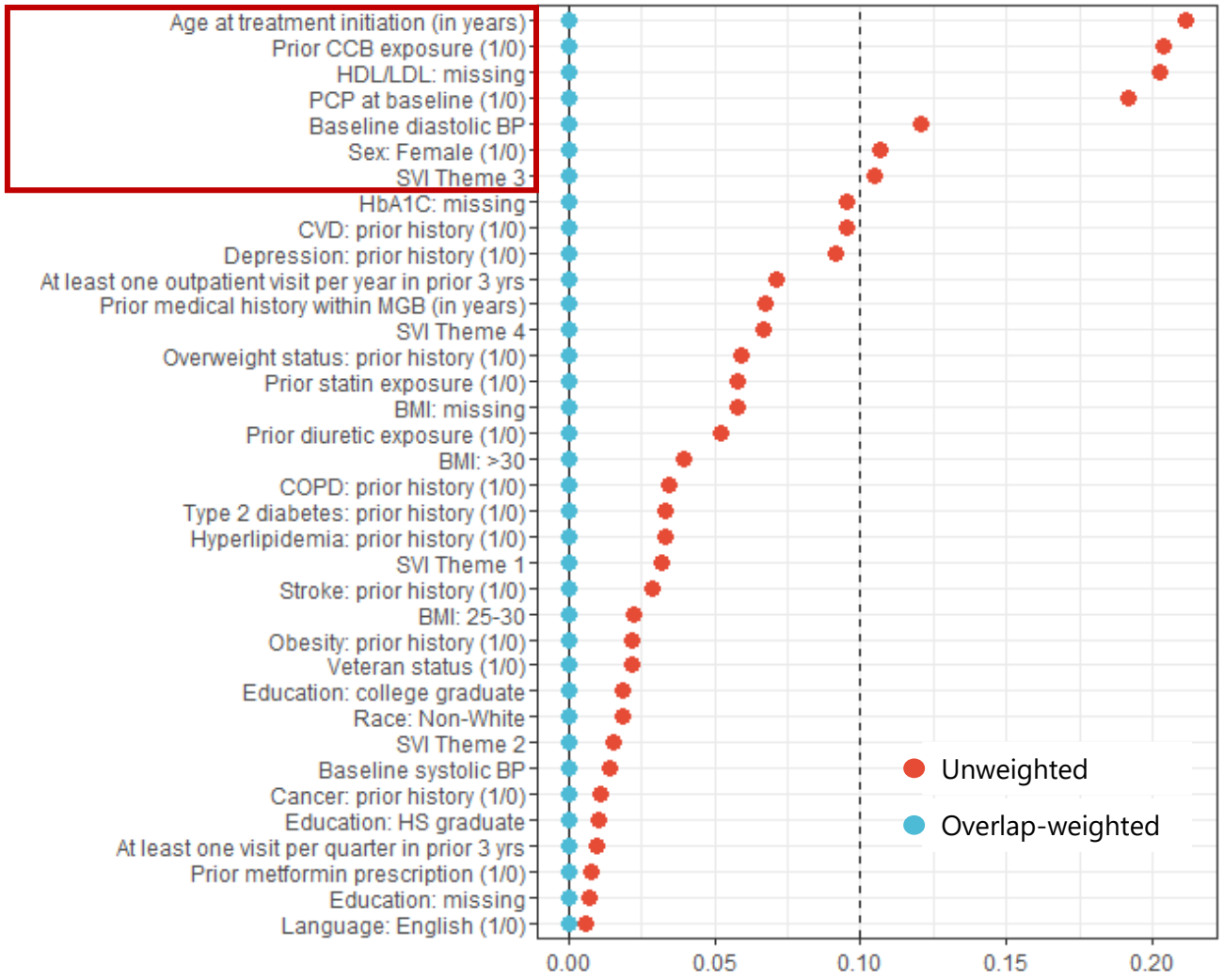
Large overlap between the two arms, enabling us to proceed with the target trial internally

Assessment of covariate balance



1. Main **differences before weighting**: age, prior exposure to calcium channel blockers (CCB), presence of a primary care physician (PCP), etc.

Assessment of covariate balance



1. Main **differences before weighting**: age, prior exposure to calcium channel blockers (CCB), presence of a primary care physician (PCP), etc.

2. Elimination of measured confounding bias **after weighting** the contribution of each patient.

How do the two arms compare after balancing and accounting for competing death?

First metric: hazard ratio (HR), time-independent

HR < 1: ACEi better than ARB initiation
HR = 1: no difference
HR > 1: ACEi worse than ARB initiation

Estimated hazard ratios suggest a detrimental effect of ACEi initiation w.r.t. MCI/dementia onset, relative to ARB initiation

Event type	Hazard Ratio
MCI/dementia onset	**HR = 1.10** 95% CI = [1.01 – 1.21]

HR < 1: ACEi better than ARB initiation
HR = 1: no difference
HR > 1: ACEi worse than ARB initiation

Estimated hazard ratios suggest no difference between ACEi and ARB initiation w.r.t. competing death

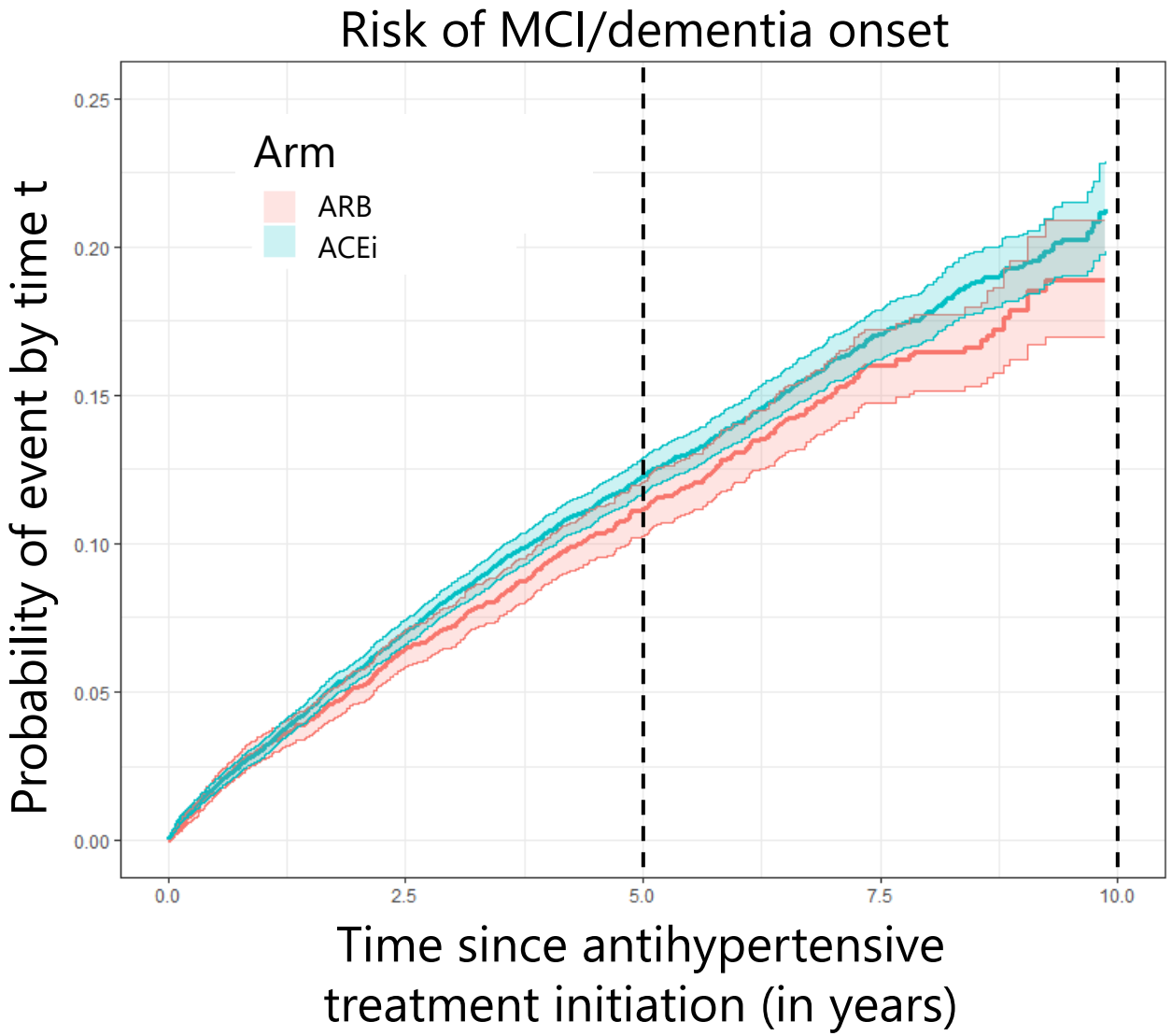
Event type	Hazard Ratio
Dementia onset	**HR = 1.10** 95% CI = [1.01 – 1.21]
Death before dementia	HR = 1.05 95% CI = [0.94 – 1.16]

HR < 1: ACEi better than ARB initiation
HR = 1: no difference
HR > 1: ACEi worse than ARB initiation

Second metric: cumulative risk, time-dependent

Probability of an event of a certain type occurring by time t

1pp higher 5-year risk of MCI/dementia onset among ACEi vs. ARB initiators



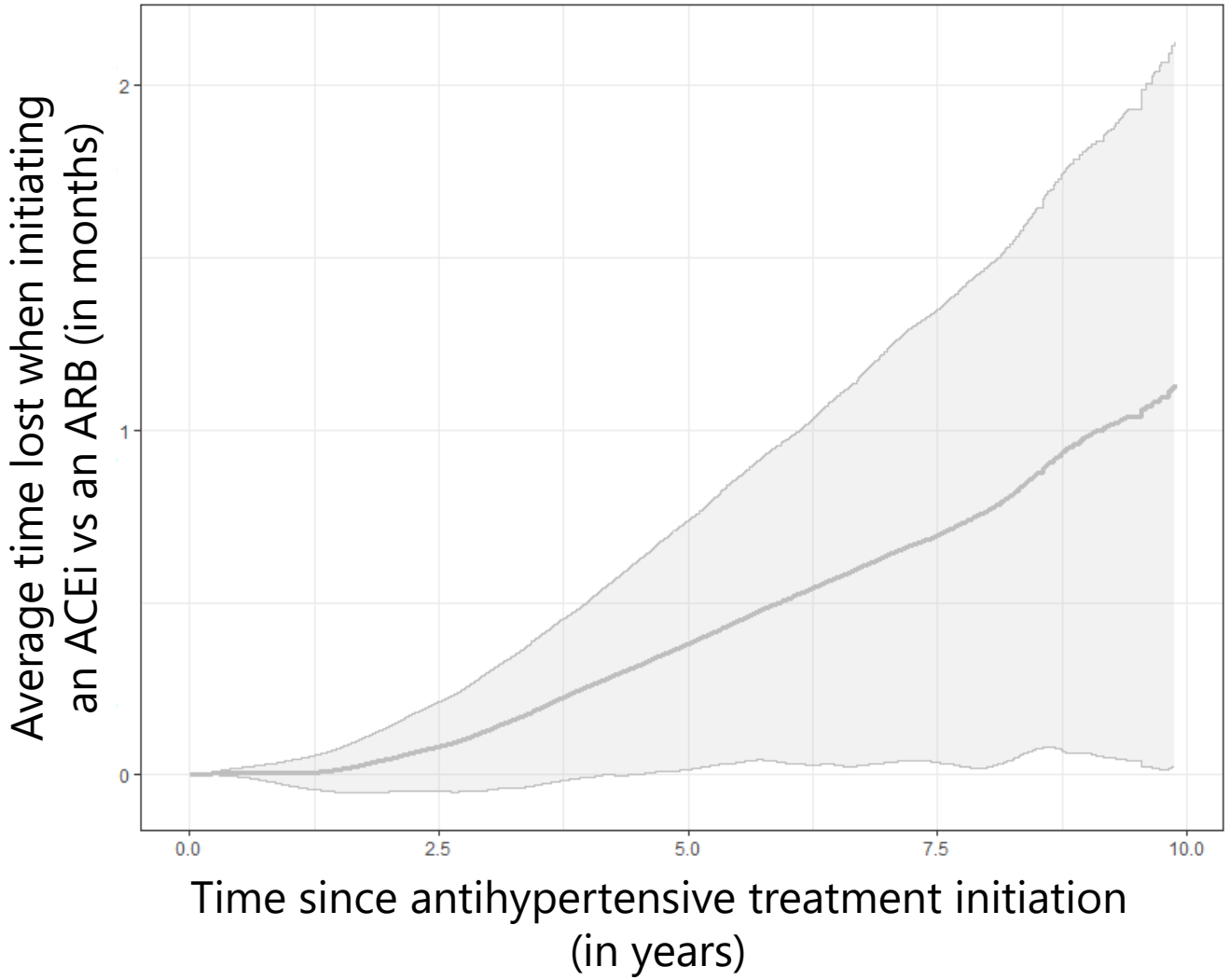
When <u>not</u> assuming proportional hazards, risk differences were estimated to:

<u>Year 5</u>
1.12pp (0.048 to 2.19)

<u>Year 10</u>
2.36pp (-0.45 to 4.68)

**95% CIs obtained via Bayesian bootstrap (500 iterations)*

Up to 4 months of MCI/dementia-free time lost under ACEi vs. ARB initiation



Clinical impact

Estimated risk differences can be translated into an average dementia-free time loss.

- Overall: up to 2 months
- Among men: up to 4 months

Potential public health implications & work needed

Small effect at the individual level
Estimated loss of <6 MCI/dementia-free months, over a 10-year period, among people initiating an ACEi vs an ARB

Potentially important implications at the population level
55 million US adults prescribed an ACEi for chronic hypertension

⟹ Replications in larger EHR systems and mechanistic studies are needed to stress-test the results of this single-center target trial emulation.

Limitations

1. Potential for residual confounding (e.g., lifestyle factors).
2. Absence of linkage to claims data to check medication dispensing and adherence.
3. Measurement errors affecting the definition and timing of dementia outcomes.
4. Lack of representativity of the considered patient population and implications for generalizability outside the Mass General Brigham healthcare system.

Next steps

1. Identify subgroups of patients least/most affected.
2. Conduct a per-protocol analysis in EHR linked with claims data.
3. Understand the potential mediating role played by blood pressure control.
4. Implement multi-arm target trials by drug class and brain penetrance.
5. Contrast with other inferential strategies (e.g., physician prescribing preferences as instrumental variables).
6. Develop a framework to federate target trial emulations across healthcare systems and extend to other drug classes.

Acknowledgements

US

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Max Sunog (MGB)

UK, Imperial

Ioanna Tzoulaki
Youssef Hbid
Bowen Su

Israel, Haifa

Bella Lagun








Thanks for your attention!
Any questions?

Feel free to reach out:
marie.x.charpignon@kp.org

Appendix

Target trial specification & emulation

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The causal contrast is defined based on the single-world ($a = 0$ vs. $a = 1$) causal quantities of interest, i.e., the **cumulative risk R** of experiencing dementia onset ($k = 1$) or dying before ($k = 2$).

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H1: Conditional exchangeability
H2: Positivity

H3: Conditionally independent censoring
The potential right-censoring times C^a are conditionally independent of the potential outcome pairs, given baseline covariates X. I.e., for any arm a:

$$C^a \perp (U^a, F^a) \mid X$$

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H4: Stable Unit Treatment Value Assumption (SUTVA)

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1. No interference: The potential outcomes of any given patient do not vary with the treatments assigned to other patients.

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H4: Stable Unit Treatment Value Assumption (SUTVA)

1. No interference: The potential outcomes of any given patient do not vary with the treatments assigned to other patients.
2. Consistency: For each patient, there are no different versions of each treatment that lead to different potential outcomes.

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$$\sum_{i=1}^{n} \widehat{w_i}\, \mathbb{I}(E_i = \boldsymbol{k}) \left(A_i - \frac{\sum_{j=1}^{n} \widehat{w_j} A_j \exp(\boldsymbol{\beta_k} A_j) \mathbb{I}(T_j \geq T_i)}{\sum_{j=1}^{n} \widehat{w_j} \exp(\boldsymbol{\beta_k} A_j) \mathbb{I}(T_j \geq T_i)} \right) = 0$$

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Events

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Follow-up times

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For $k \in \{1,2\}$, it is defined as a weighted version of the Breslow-type estimator:

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For $k \in \{1,2\}$, it is defined as a weighted version of the Breslow-type estimator:

$$\forall\, t > 0\colon\ \widehat{H_k^0}(t) = \sum_{\{i\colon E_i = k, T_i \le t\}} \frac{\widehat{w_i}}{\sum_{j=1}^{n} \widehat{w_j} \exp\left(\widehat{\beta_k} A_j\right) \mathbb{I}\left(T_j \ge T_i\right)}$$

Estimator of the log hazard ratio $\widehat{\beta_k}$ from Step 1

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Step 3: Estimator of the **cause- and world-specific** cumulative risk function $\widehat{R_k^a}$

For $k \in \{1,2\}$, it is given by:

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For $k \in \{1,2\}$, it is given by:

$$\forall\, t > 0\colon\ \widehat{R_k^a}(t) = \sum_{\{i\colon E_i = k, T_i \le t\}} \frac{\widehat{w_i} \exp\left(-\widehat{H_1^0}(T_i)\exp\left(\widehat{\beta_1} a\right) - \widehat{H_2^0}(T_i)\exp\left(\widehat{\beta_2} a\right)\right)}{\sum_{j=1}^{n} \widehat{w_j} \exp\left(\widehat{\beta_k} A_j\right) \mathbb{I}\left(T_j \ge T_i\right)}$$

Plug-in estimator of the survival function S^a

Target trial specification & emulation

1. Eligibility criteria
2. Treatment strategies
3. Treatment assignment
4. Outcome definition
5. Follow-up definition
6. Causal contrasts
7. Statistical analysis
    a. Assumptions
    b. Choice of weights
    c. Estimation

Step 4: Estimator of the **cause- or event-specific** risk difference function $\widehat{RD}_{\boldsymbol{k}}$

For $\boldsymbol{k} \in \{1,2\}$, it is given by:

$$\forall t > 0\colon\ \widehat{RD}_{\boldsymbol{k}}(t) = \widehat{R}^{\boldsymbol{1}}_{\boldsymbol{k}}(t) - \widehat{R}^{\boldsymbol{0}}_{\boldsymbol{k}}(t)$$