

Two-step modelling approach of time to event and cognitive decline to inform Alzheimer's disease prevention trials



Giulia Lestini¹, Amy Racine¹, Ines Paule¹, Chrystel Feller¹, Kostas Biliouris², Etienne Pigeolet¹, Cristina Lopez Lopez¹, Ana Graf¹, Angelika Caputo¹

¹Novartis Pharma AG, Basel, Switzerland, ²Novartis Institute for Biomedical Research, Cambridge, MA, USA

Background

Alzheimer's disease (AD) trials in the prevention setting are of long duration due to the fact that several years may be required for detecting first signs of cognitive decline in asymptomatic patients. Optimal clinical trial designs to evaluate innovative treatments[1] are thus needed to test disease-modifying interventions in the AD prevention setting.

Objective

- To develop a model to support the design of such clinical trials in participants at risk of developing mild cognitive impairment (MCI) or dementia due to AD
- To assess the performance of two different endpoints in terms of statistical power
 - time to MCI or dementia diagnosis
 - Alzheimer's prevention initiative Preclinical Composite Cognitive score (APCC)[2].

Method

Model building

Time to event model

- A time to event (TTE) model describing the time to first diagnosis of MCI or dementia due to AD using parametric survival functions
 - The TTE model was fitted to longitudinal data from the National Alzheimer's Coordinating Center (NACC) and data collected from three cohort studies (ROS, MAP and MARS) of aging and dementia at the Rush Alzheimer's Disease Center

APCC models

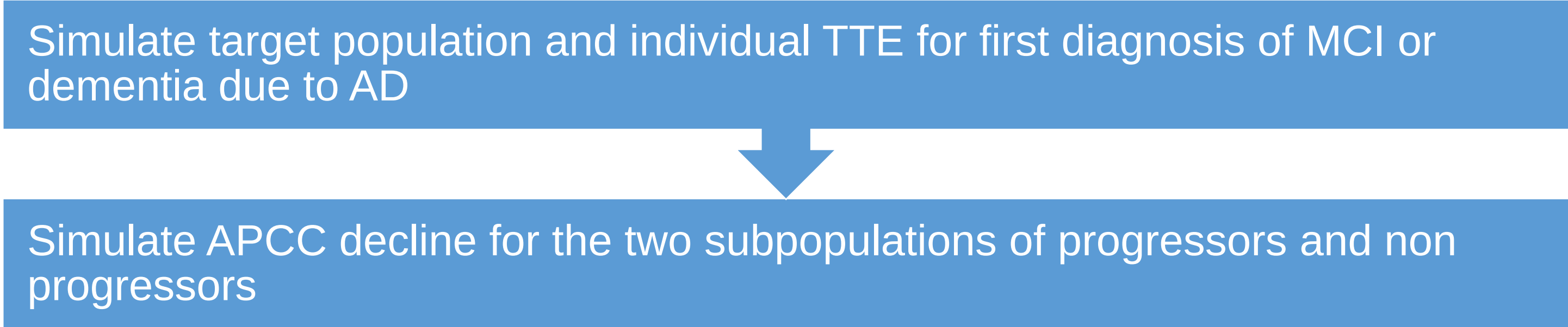
- Two subpopulations in the Rush cohorts were identified:
 - "progressors": subjects with first diagnosis of MCI/dementia within 8 years
 - "non-progressors": subjects not diagnosed or only diagnosed after 8 years
- Mixed-effects models describing the progression of APCC scores over time were developed and fitted to these 2 subpopulations in the Rush cohorts
 - nonlinear-mixed effects model was fitted to progressors
 - linear-mixed effects model was fitted to the non-progressors
- A time scale anchored at the time to MCI or dementia diagnosis predicted by the TTE model was used for the progressors model

Covariates and structural model validation

- Clinically relevant covariates also including the Apolipoprotein E (APOE-ε4) status, were tested for statistical significance in both models using backward elimination based on Akaike's information criterion
- TTE model survival functions tested: Weibull, exponential, Gompertz, and piece-wise exponential
- APCC model structure validated by comparison of linear and quadratic models (in non-progressors model) and also power model (in progressors model)

Clinical trial simulation strategy

Figure 1: Schema of AD prevention model



Scenarios for power assessment

- 1000 clinical trials were simulated to investigate power separately for the 2 endpoints with varying sample size and for a 5-year follow up
- Each run simulated placebo (natural course) as well as multiple active arms corresponding to different treatment effects formulated as hazard ratio (HR) from 0.9 to 0.6, i.e. risk reduction of 10% to 40% of developing MCI or dementia within a 5-year study
 - HR = 0.7 corresponds to around 1 year delay in 5 years (the 5 years risk for placebo will only be observed about 1 year later in active)

Conclusions

- This two-step modelling approach of time to MCI or AD diagnosis and APCC decline has been successfully used to design clinical trials in the AD prevention setting
 - The model shows good internal validity and allows comparing the performance of different endpoints in terms of statistical power
 - Further refinements of the model, e.g. including amyloid-beta and tau as covariates are objectives of future research

Results

Evaluation of the structural model

Figure 2: Comparison of survival functions for TTE model

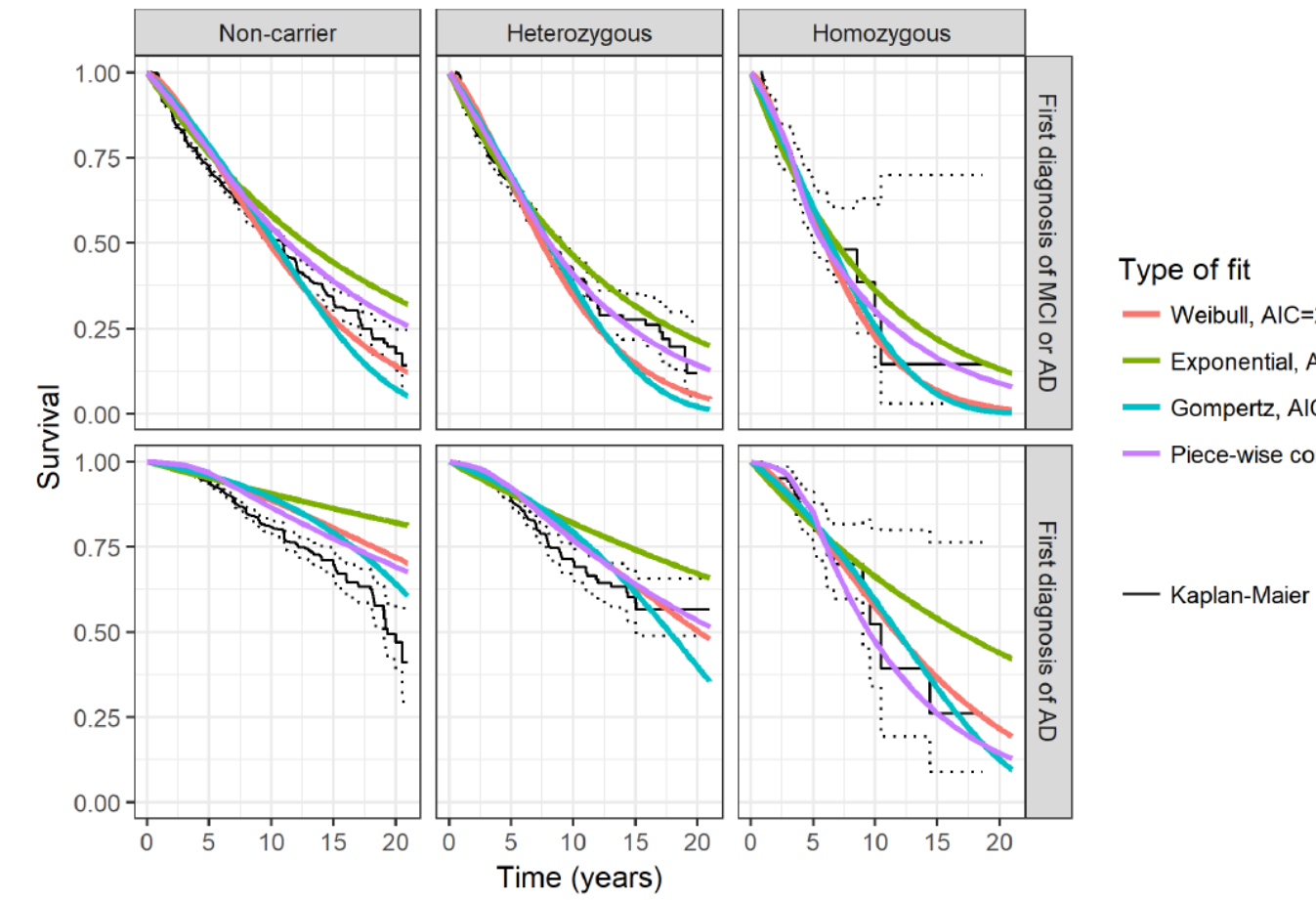
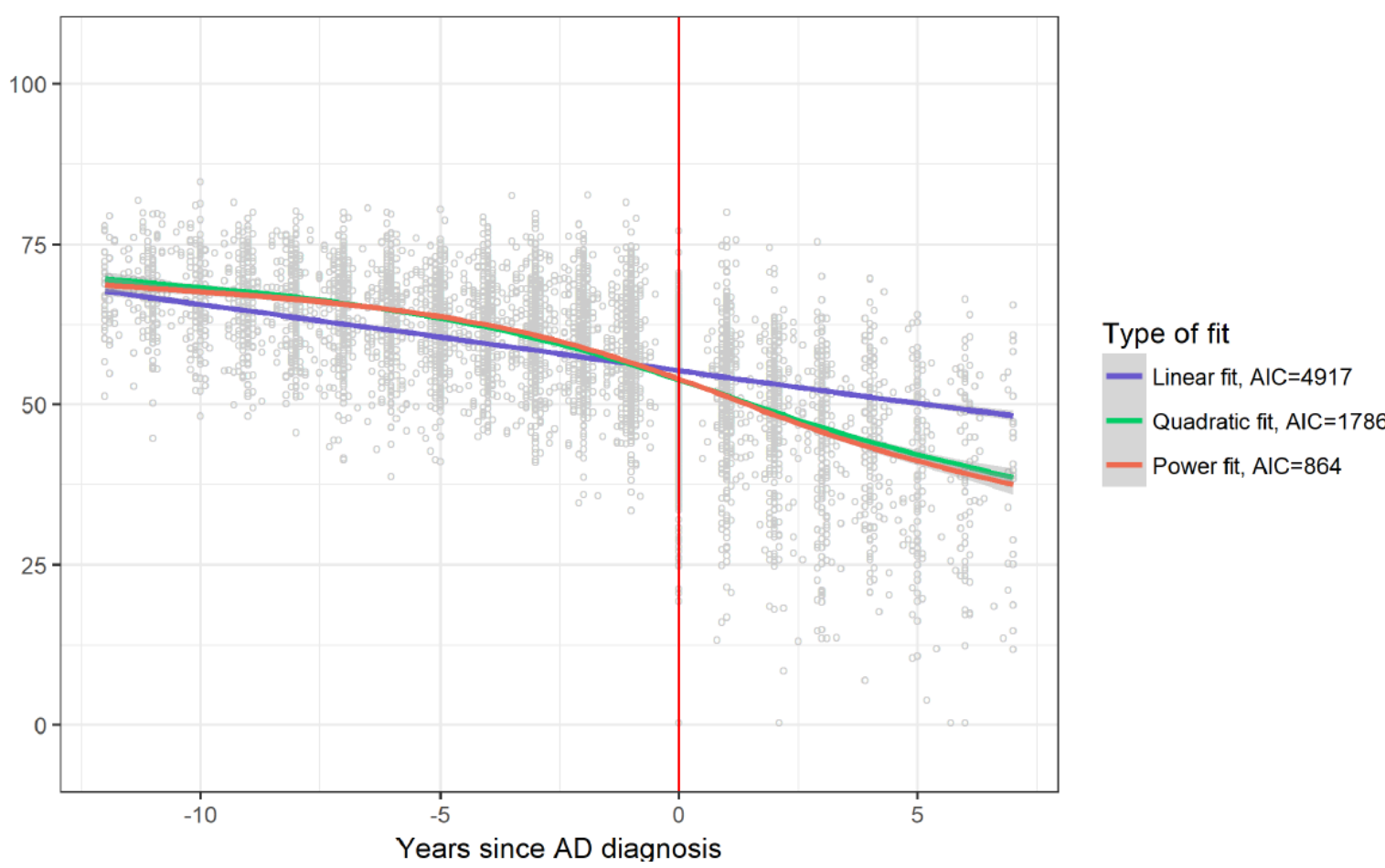


Figure 3: Model comparison for APCC model for progressors



- TTE model (Figure 2): Weibull model performed best in terms of AIC among the other tested survival function
- APCC model for progressors (Figure 3): power model performed best in terms of AIC
- APCC model for non-progressors (graphs not reported): linear model performed best in terms of AIC

Covariates selection

Table 1: Covariates selected by backward elimination based on AIC

	APCC at BL	Education years	APOE4 status	Sex	Age
TTE model	x	x	x		x (at BL)
APCC model for progressors					
Intercept	x	x		x	x (at event)
Rate	x	x	x		
APCC model for non-progressors					
Intercept	x	x		x	x (at BL)
Rate	x	x	x	x	x (at BL)

Clinical trial simulations and power assessment

- Power of the TTE endpoint at the projected analysis time was acceptable (range from 70% to 94%) for the tested HR (from 0.9 to 0.6, i.e. risk reduction of 10% to 40%)
- Power of APCC was smaller compared to TTE in simulation, but may increase with smaller variability in homogenous population in a clinical trials setting

References

- Reiman EM, et al. *Biomark Med.* 2010; 4(1): 3–14
- Langbaum JB et al. *Alzheimer's & Dementia.* 2014; 10(6):666-74

Acknowledgements

This work was done at Novartis to support the Generation Program, clinical studies conducted in collaboration with Banner Alzheimer Institute and Amgen. The authors would like to thank Neva Coello (Novartis) and the Analytica Laser group.

Disclosures

Poster presented at Population Approach Group Europe (PAGE), May 29 – June 1, 2018, Montreux, Switzerland.