SUPPLEMENTAL MATERIAL

Data S1.

Supplemental Methods

Linear mixed-effects model building and selection.

We used all NT-proBNP measurements that occurred prior to the primary endpoint (n=2009), with a median of 4 measurements per patient. We started with a LME with linear and quadratic time evolutions, a nonlinear effect of age using natural cubic splines with 3 degrees of freedom, the main effects of sex, diagnosis, NYHA class, medication use, rhythm, systemic ventricular function, BMI, saturation, re-intervention and logeGFR, and the interactions of time with sex and diagnosis (Model 1).

We first expanded the random-effects structure, while keeping the same fixed effects, in order to appropriately model the correlations in the repeated NT-proBNP measurements. We therefore included the linear random slopes term (Model 2) and tested whether this improved the fit of the model by using a likelihood ratio test, which was not the case (P=0.323). Therefore, we continued with a model with only random intercepts.

To define the fixed part of the model, we subsequently tested whether the interaction terms had an important contribution to the fit of the model. To this end, we refitted Model 1 under maximum likelihood (instead of the default restricted maximum likelihood) and then fitted another model without the interaction terms (Model 3). The results suggested that the effects of time do not differ between men and women, and between patients with a moderate or complex diagnosis (P=0.249). We continued by performing the omnibus test for all nonlinear terms in the model. We therefore fitted the model that excluded all nonlinear terms (Model 4) and compared this with Model 3 using the likelihood ratio test. This indicated that the nonlinear terms did not have a significant contribution to the model (P=0.096).

Therefore, the final selected model for the $\log_2$ transformed serial NT-proBNP measurements was a random intercepts LME with a linear time evolution, and main effects of age (linear), sex, diagnosis, NYHA class, medication use, rhythm, systemic ventricular function, BMI, saturation, re-intervention and logeGFR. A schematic overview of the LME model building and selection is presented in Supplemental Table 1. This model was refitted with restricted maximum likelihood and further used for the estimation of the temporal NT-proBNP evolution. Of note, the joint models were estimated using a Bayesian framework.

Table S1. Linear mixed-effects model building and selection.

NT-proBNP model	Fixed	Random	LRT	Compared with (method)
1	logBNP ~ (obstimeyr + I(obstimeyr^2)) * (sex + diagnosis) + ns(age,3) + NYHA + medication + rhythm + systfunc + BMI + saturation + reintervention + logeGFR	~ 1 | id		
2	Equal to model 1	~ obstimeyr | id	P=0.323	Model 1 (REML)
3	logBNP ~ (obstimeyr + I(obstimeyr^2)) + sex + diagnosis + ns(age,3) + NYHA + medication + rhythm + systfunc + BMI + saturation + reintervention + logeGFR	~ 1 | id	P=0.249	Model 1 (ML)
4	logBNP ~ obstimeyr + sex + diagnosis + age + NYHA + medication + rhythm + systfunc + BMI + saturation + reintervention + logeGFR	~ 1 | id	P=0.096	Model 3 (ML)

Figure S1. Individual NT-proBNP profiles in patients without and with the primary endpoint.

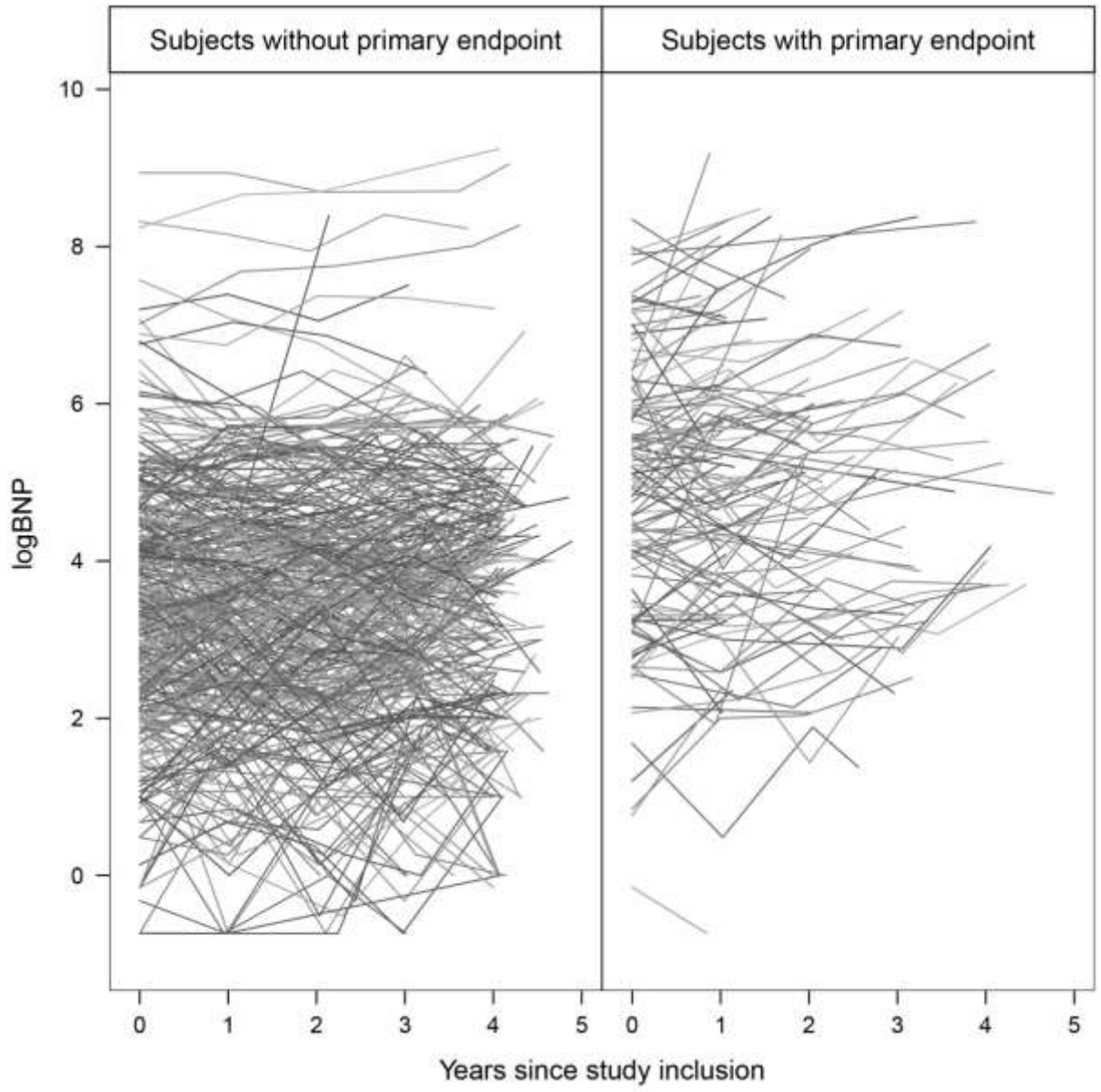


Figure S2. Individual NT-proBNP profiles in patients without and with the secondary endpoint.

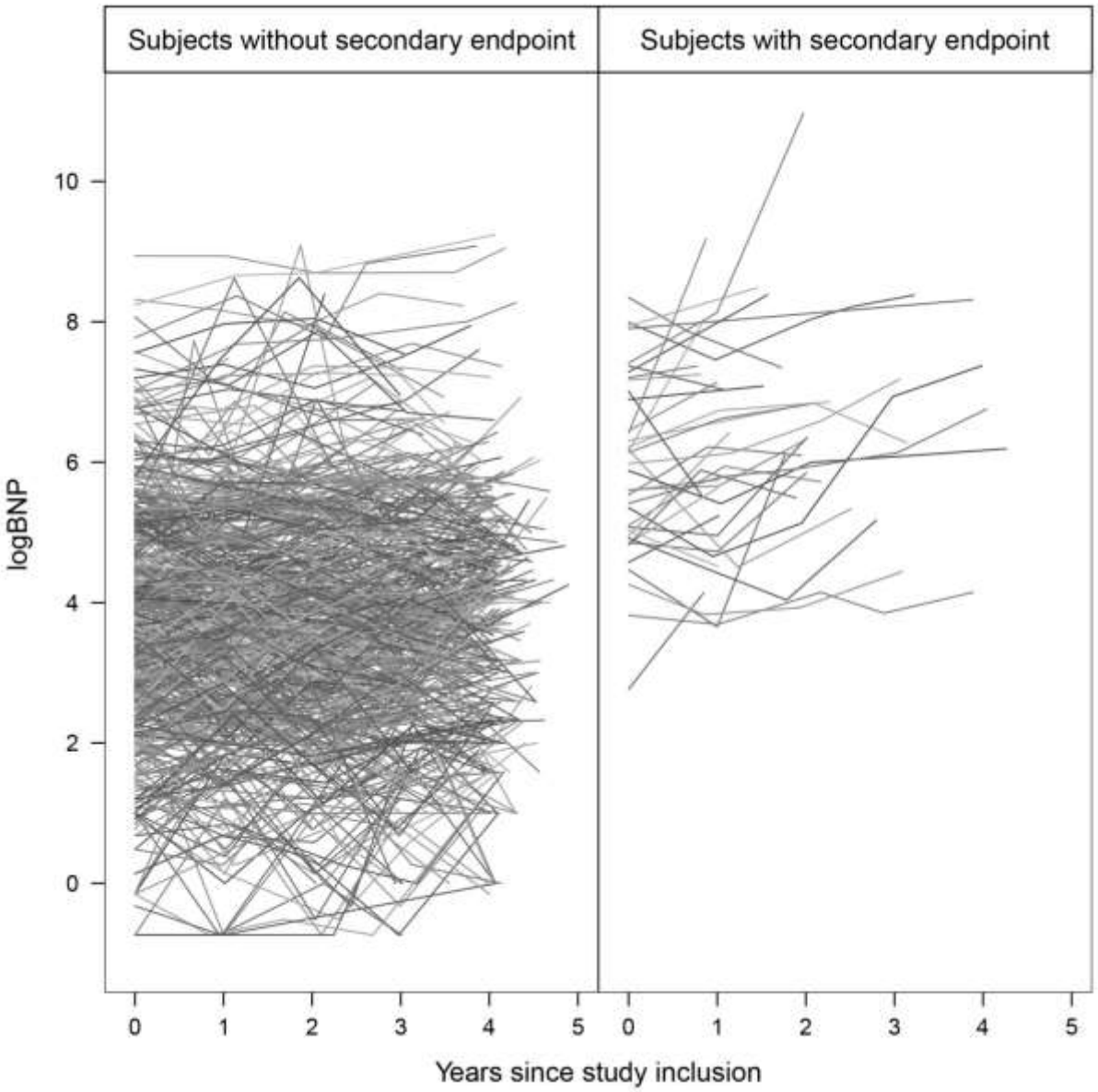


Figure S3. NT-proBNP profiles in patients with a surgical or percutaneous valve intervention (at time point 0).

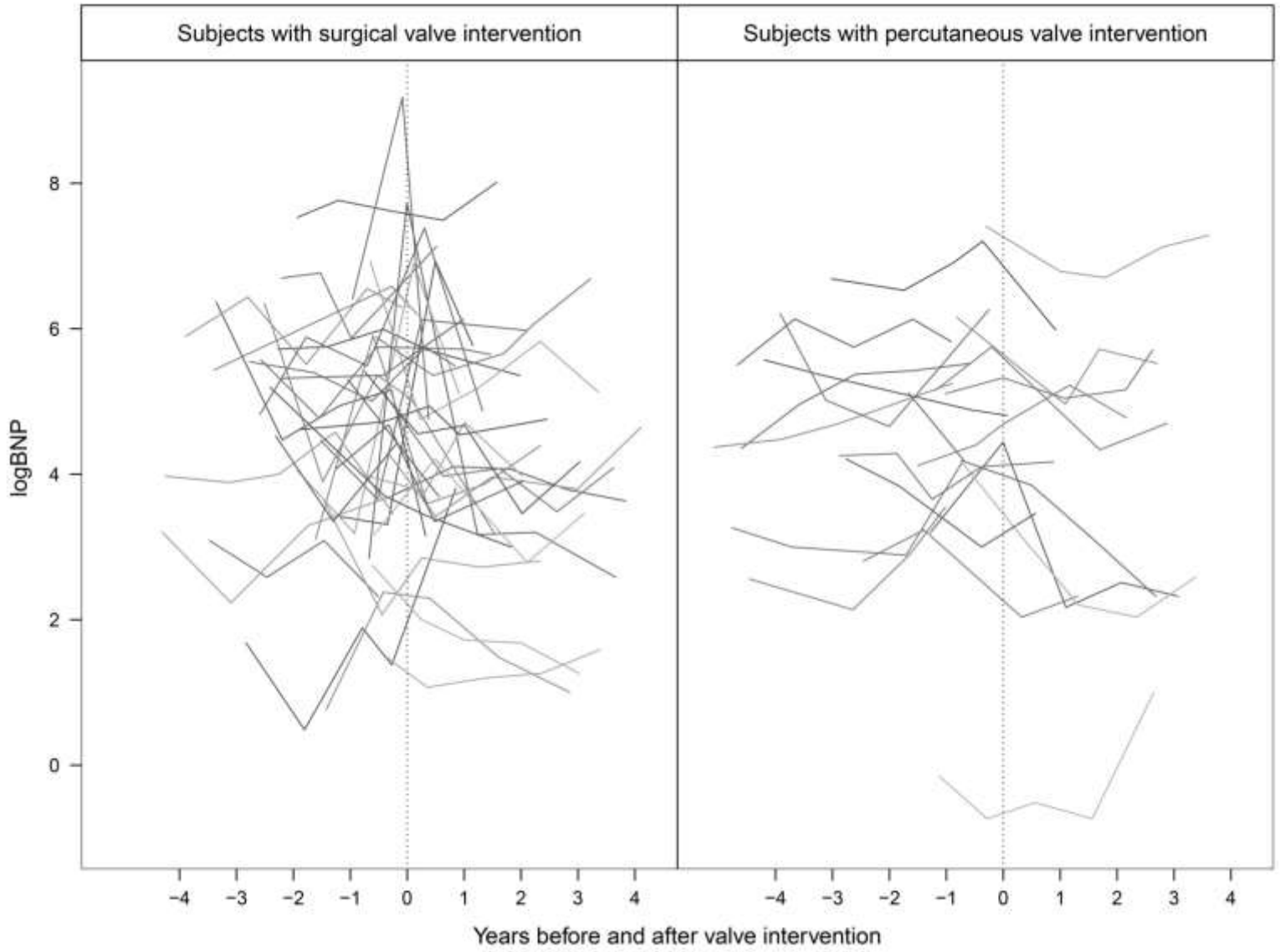
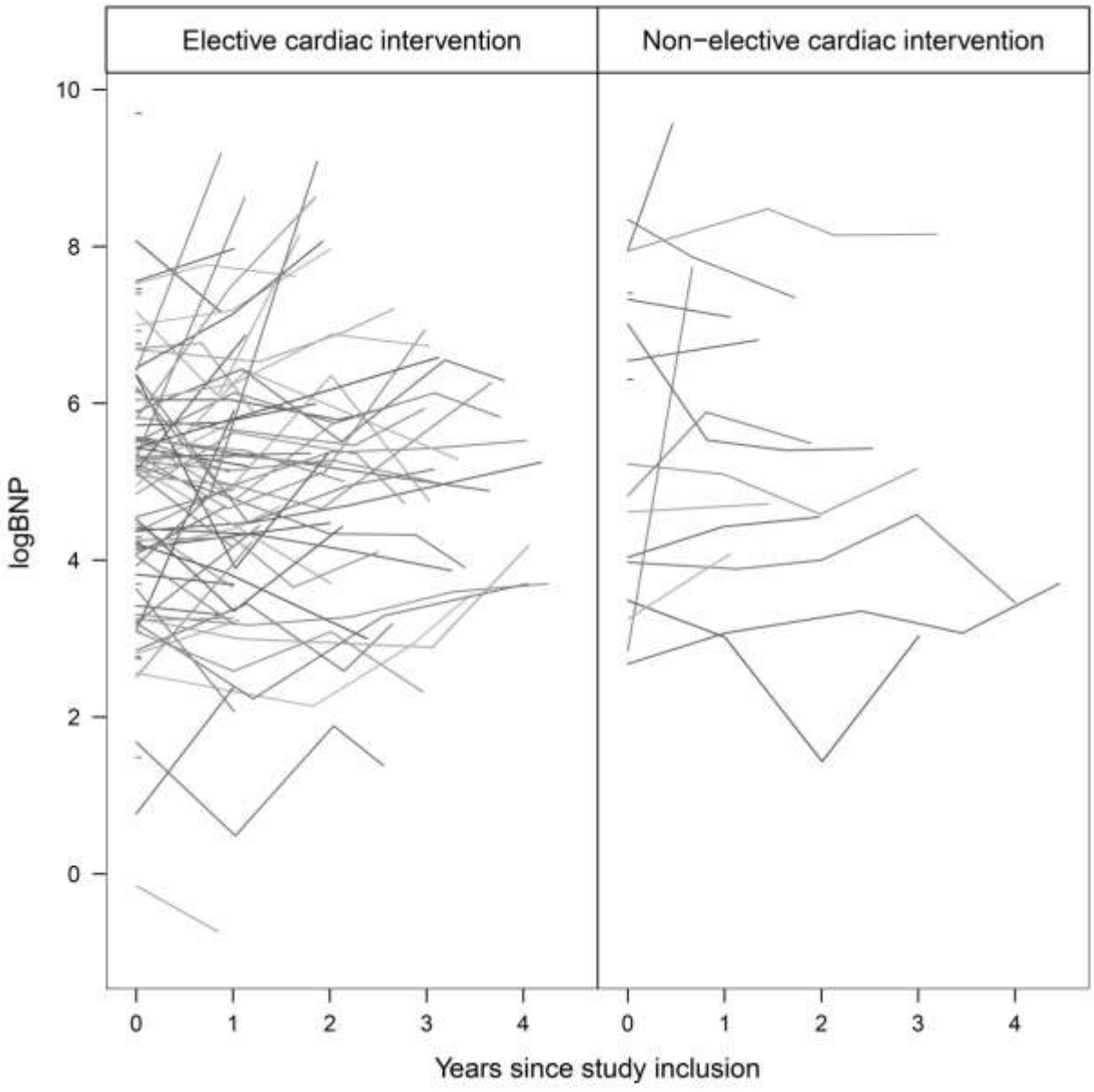
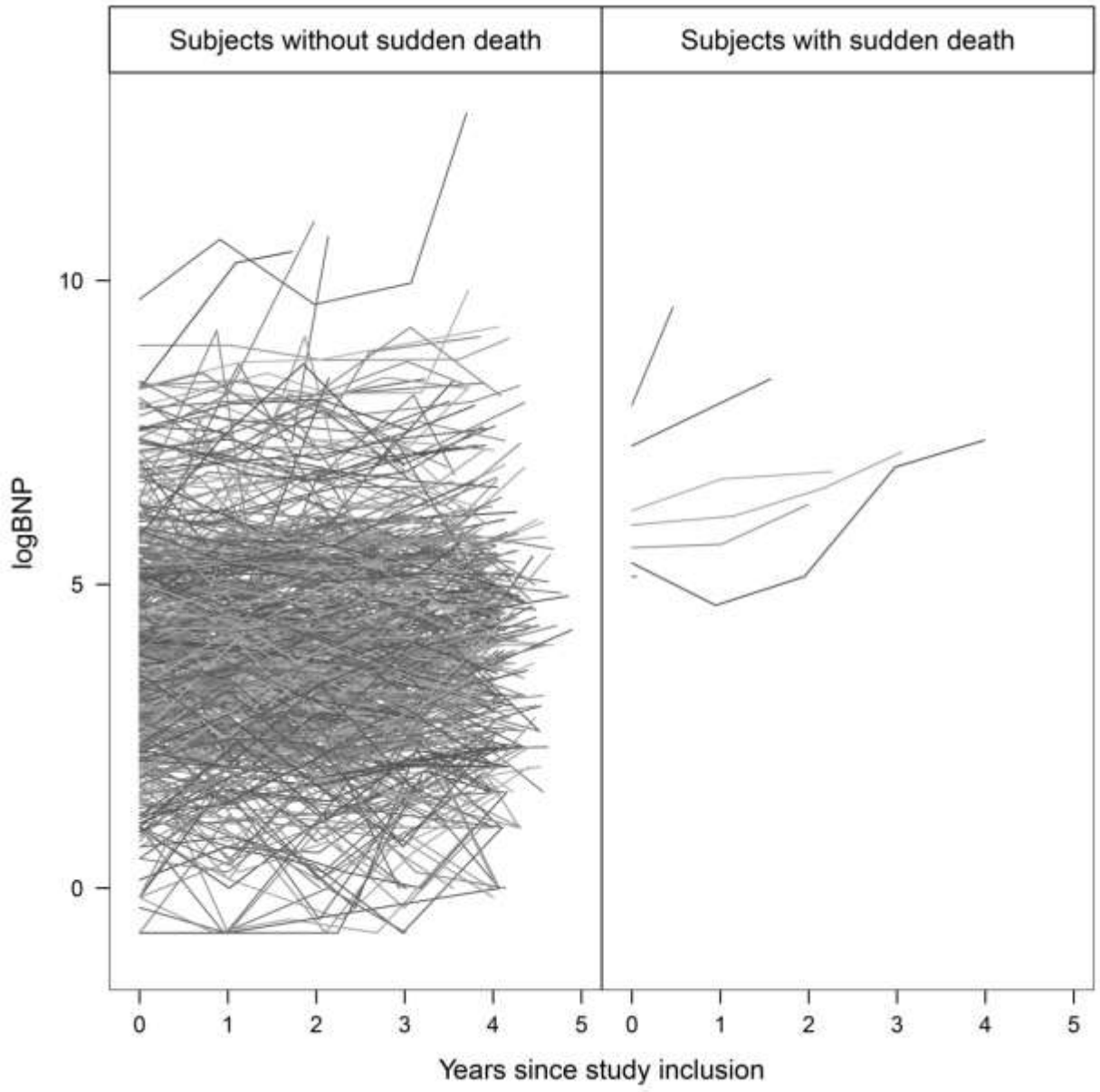


Figure S4. NT-proBNP profiles in patients with elective versus non-elective cardiac interventions.



Of the 113 cardiac interventions, 17 were non-elective (pacemaker or ICD implantation, n=10; surgical aortic valve replacement, n=4; percutaneous pulmonary valve dilatation, n=1; coronary intervention, n=1; ablation, n=1). No clear differences in the NT-proBNP profiles were observed, probably because the group of patients with a non-elective intervention was relatively small and heterogeneous.

Figure S5. NT-proBNP profiles in patients with sudden cardiac death.



The 7 patients with sudden cardiac death had higher NT-proBNP levels at baseline that increased over time in all patients. Because of the low (expected) number of patients with sudden cardiac death, we did not aim to make predictions for this specific endpoint.