Online file 1. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
▪ Age 18 years or older	▪ Plasma CA125 ≤35 U/ml
▪ At least 1 episode of AHF in the last 180 days	▪ Life expectancy <12 months due to other diseases different from HF
▪ Demonstrates functional NYHA status of class ≥II at the moment of enrollment	▪ Having undergone a cardiac transplantation, coronary revascularization procedure (PCI and/or CABG) or cardiac valve replacement in the past 3 months
▪ Objective evidence, either during the index admission or at least 180 days before enrollment, of a structural or functional abnormality of the heart at rest, defined as: NT-proBNP >1000 pg/ml or BNP >100 pg/ml or echocardiographic abnormalities congruent with HF diagnosis such as: systolic LV dysfunction (LVEF <50%); LV hypertrophy (defined as septum or LV posterior wall thickness ≥12 mm or LV mass index >104 g/m^2 in women or 116 g/m^2 in men); E/e' ratio >15 or; significant valvular heart disease (moderate to severe)	▪ Angina pectoris higher than class II (CCS Classification)
▪ A plasma CA125 value >35 U/ml in a recent test evaluation (at least 30 days before enrollment, and preferably assessed before hospital discharge)	▪ Pregnancy at the moment of enrollment
▪ Patient must be capable of understanding and signing an informed consent form	▪ Valvular heart disease already scheduled for surgical intervention
	▪ Severe chronic obstructive and/or restrictive pulmonary disease, requiring continuous oxygen administration
	▪ Serum creatinine level >3 mg/dl or chronic renal insufficiency on dialysis treatment
	▪ Patients receiving resynchronization therapy during the index admission
	▪ Significant concurrent medical diseases including cancer or a history of cancer within 5 years of entering the screening period, endometriosis, cirrhosis, acute coronary syndrome within 6 months, uncontrolled hypertension, history of HIV infection, or a significant active infection
	▪ Participating in another randomized study

AHF: acute heart failure; BNP: brain natriuretic peptide; CA125: antigen carbohydrate 125; CABG: coronary artery bypass graft; CCS: Canadian Cardiovascular Society; HF: heart failure; LV: left ventricle; LVEF: left ventricular ejection fraction; NT-proBNP: amino-terminal pro-brain natriuretic peptide; NYHA: New York Heart Association; PCI: percutaneous coronary intervention;

Online file 2. CA125-guided management algorithm

Randomization visit

- Consider use of statins in all patients, especially at low doses.
- Maintain LDD if clinical stability. Consider increasing LDD if symptoms and signs of congestion persist.

Post-randomization visits (per-protocol)

- As per-protocol, all patients undergoes a clinical, echocardiographic and lab evaluation at V1 (30-day), V2 (1-month), and V3 (1-year).
- CA125 and NT-proBNP will be routinely measured at each of those visits.

Management algorithm

CA125 returns to normal values (≤ 35 U/ml)

- Consider reducing LDD, especially in patients receiving high diuretic doses (FED ≥120 mg/day) and in those with evidence of worsening renal function.
- Encourage the initiation, if not prescribed, or the continuation of statin treatment if well tolerated.

CA125 decreases but remains high (>35 U/ml)

- Consider maintaining LDD or increase dose if FED <80 mg/day is currently prescribed.
- Reevaluate clinical status and CA125; consider additional outpatient visit.
- Consider increasing statin dose.
- Consider up-titrating beta-blockers and/or ACEI and/or ARB doses to maximum doses recommended
- Consider adding aldosterone antagonist if previously not administered.

CA125 increases along the course of the trial

- Consider increasing LDD and/or adding HCTZ 12.5-50 mg/day or clorthalidone 12.5-50 mg/day and/or aldosterone antagonist 12.5-50 mg/day.
- Consider additional outpatient visits.
- Consider ambulatory administration of intravenous furosemide and/or ultrafiltration techniques.
- Maximize the statin treatment if possible.
- Consider intravenous iron if iron deficiency is present.

ACEI: angiotensin converting enzyme inhibitors; ARB: angiotensin II receptor blockers; CA125: antigen carbohydrate 125; FED: furosemide equivalent dose; HCTZ: hydrochlorothiazide; LDD: loop diuretic dose.

Online file 3

Longitudinal analysis

Joint modeling (JM)[1,2]. This is a family of methods that has been developed to explicitly account for the dependence between a longitudinal outcome and survival data. Compared to the traditional Cox regression models, JM accounts for measurement error (i.e. instrument-driven error and/or biological variation) on the longitudinal outcome. Also, this method provides unbiased and more efficient estimates by correcting for informative dropout, time-dependent confounding, and by combining information from the longitudinal and survival outcomes. Internally, this type of model combines a linear mixed regression (LMR) analysis, which describes the longitudinal trajectory of the marker (longitudinal submodel), and a Cox proportional hazards model (survival submodel). In the latter model, the fitted marker trajectory from LMR is related to the hazard of the outcome through a parametric Cox analysis in which the hazard function is modeled with restricted cubic splines. Both models (LMR and Cox) are linked each other through a shared random effect parameter.

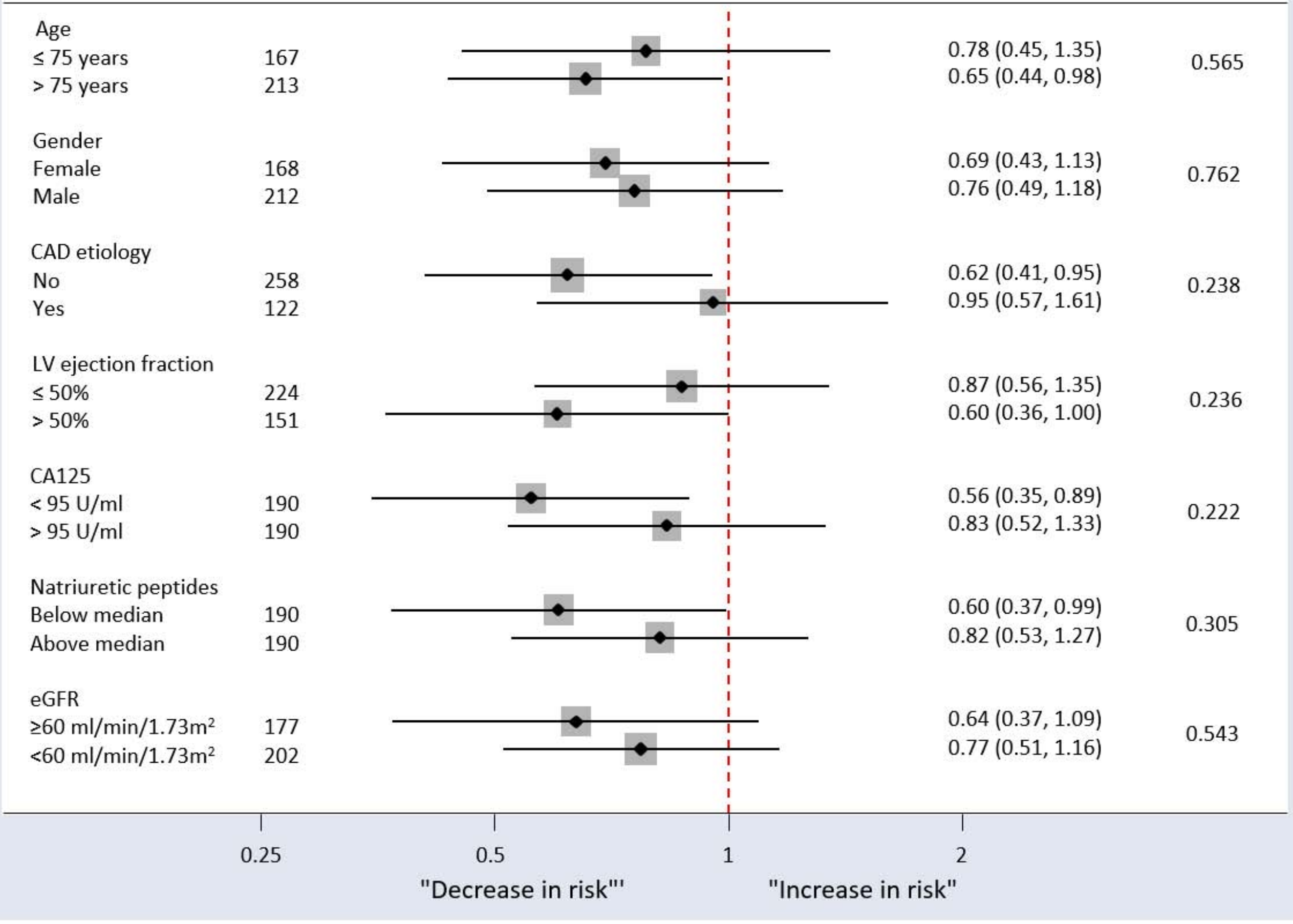
JM analysis encompasses the creation of two submodels (longitudinal and survival submodel) which can accommodate a similar or a different set of covariates. The role of the longitudinal covariates (in our case all time-varying) is to adjust the effect of the longitudinal exposure at each time point, so its effect on survival is not mediated indirectly through other risk factors. In the survival submodel, the role of the covariates is to adjust the effect of the fitted longitudinal exposure, which is modeled in the Cox model as a time-varying variable, on mortality.

References

1. Rizopoulos, D. (2012). Joint Models for Longitudinal and Time-to-Event Data with Applications in R. Chapman and Hall/CRC Biostatistics Series, Boca Raton.
2. Rizopoulos D. Comments on 'Joint modeling of survival and longitudinal non-survival data: current methods and issues. Report of the DIA Bayesian Joint Modeling Working Group'. Stat Med. 2015 Jun 30;34(14):2196-7.

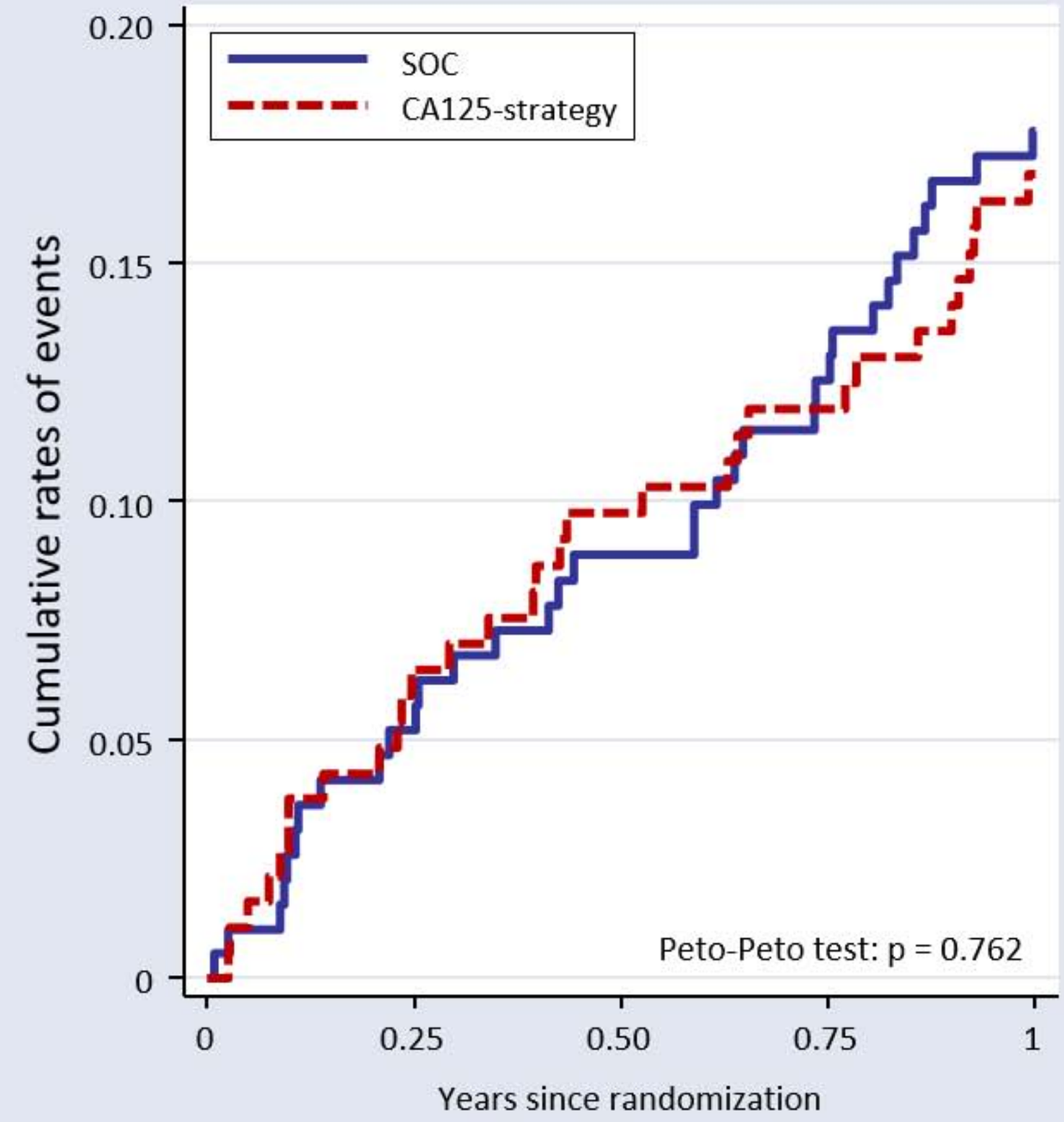
Online file 4. Subgroup analysis

Subgroup	Patients (n)	Hazard Ratio (95% CI)	Omnibus p-value
Age			
≤ 75 years	167	0.78 (0.45, 1.35)	0.565
> 75 years	213	0.65 (0.44, 0.98)	
Gender			
Female	168	0.69 (0.43, 1.13)	0.762
Male	212	0.76 (0.49, 1.18)	
CAD etiology			
No	258	0.62 (0.41, 0.95)	0.238
Yes	122	0.95 (0.57, 1.61)	
LV ejection fraction			
≤ 50%	224	0.87 (0.56, 1.35)	0.236
> 50%	151	0.60 (0.36, 1.00)	
CA125			
< 95 U/ml	190	0.56 (0.35, 0.89)	0.222
> 95 U/ml	190	0.83 (0.52, 1.33)	
Natriuretic peptides			
Below median	190	0.60 (0.37, 0.99)	0.305
Above median	190	0.82 (0.53, 1.27)	
eGFR			
≥60 ml/min/1.73m²	177	0.64 (0.37, 1.09)	0.543
<60 ml/min/1.73m²	202	0.77 (0.51, 1.16)	



CA125: carbohydrate antigen 125; CAD: coronary artery disease; eGFR: estimated glomerular filtration rate; LV: left ventricle

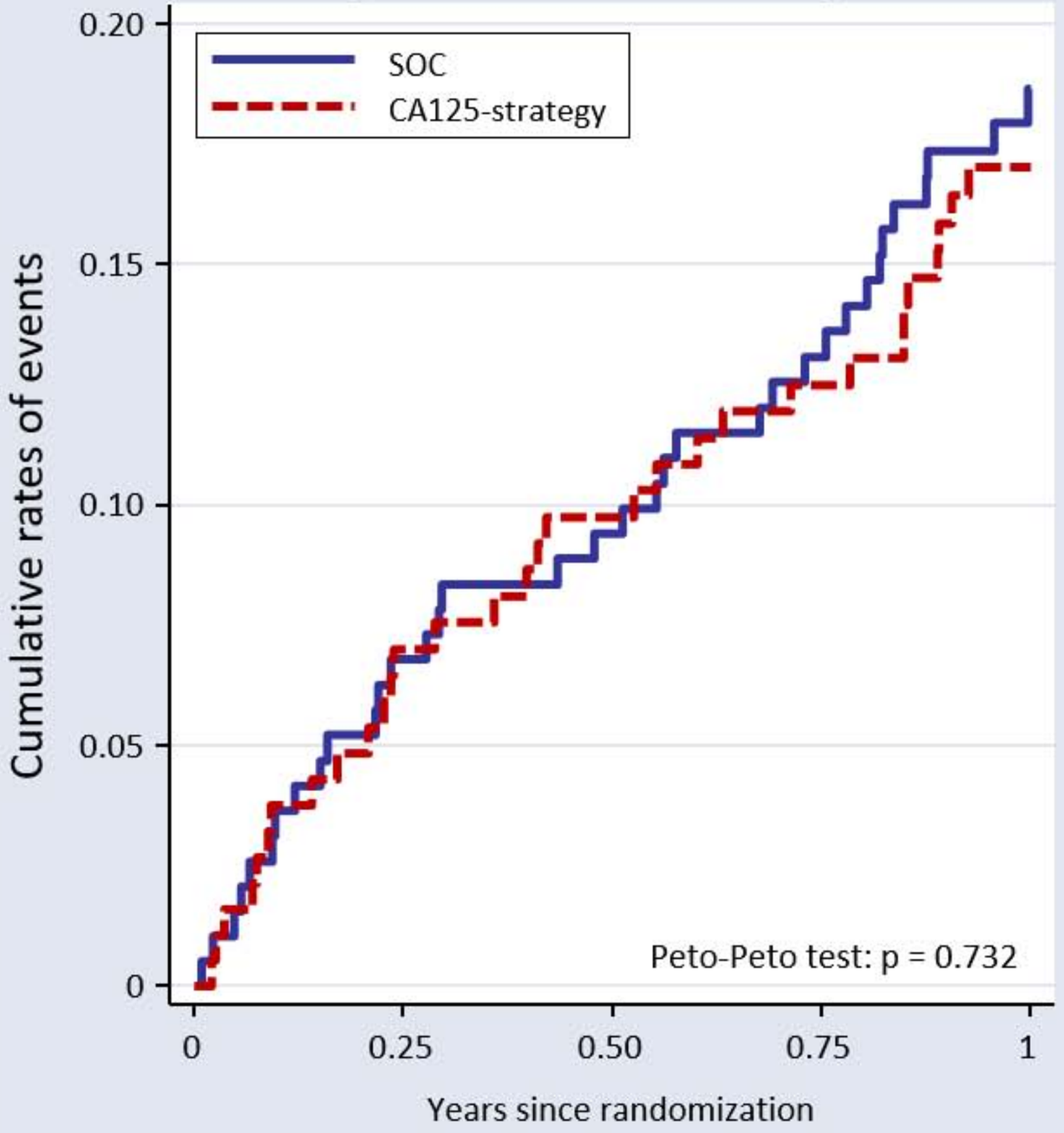
5a



Number at risk (events)

SOC	193	(10)	181	(7)	174	(7)	167	(10)	157
CA125-strategy	187	(12)	172	(6)	165	(4)	161	(9)	152

5b



Number at risk (events)

SOC	193	(13)	178	(5)	173	(7)	164	(10)	113
CA125-strategy	187	(13)	170	(5)	164	(5)	158	(8)	113

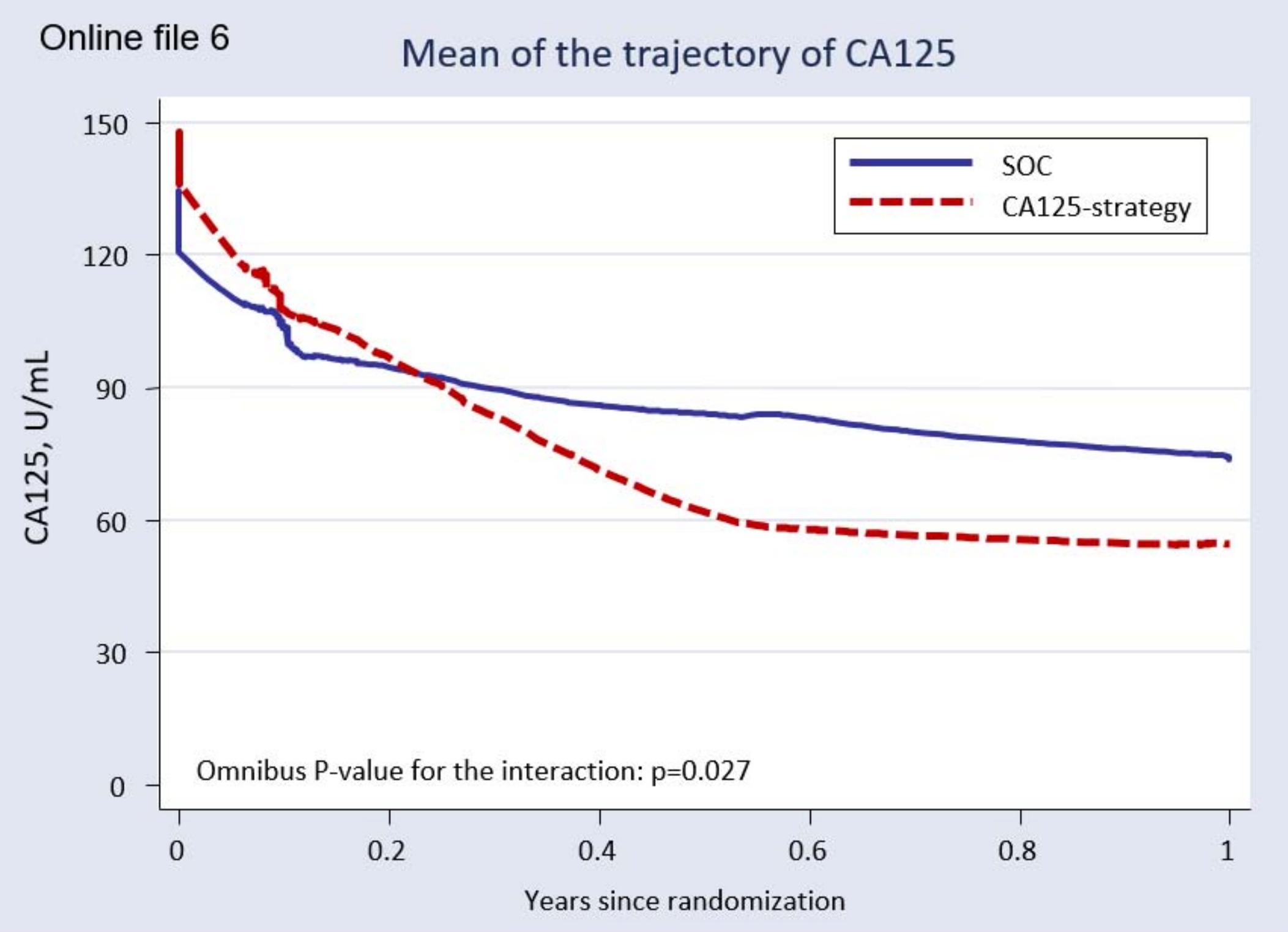
CA125: carbohydrate antigen 125; SOC: standard of care

*Time to first event endpoints

S5a. Kaplan-Meier curve for all-cause mortality (secondary endpoint).

S5b. Kaplan-Meier curve for all-cause mortality using as a follow-up time “days alive and out of the hospital” (secondary endpoint).

Online file 6

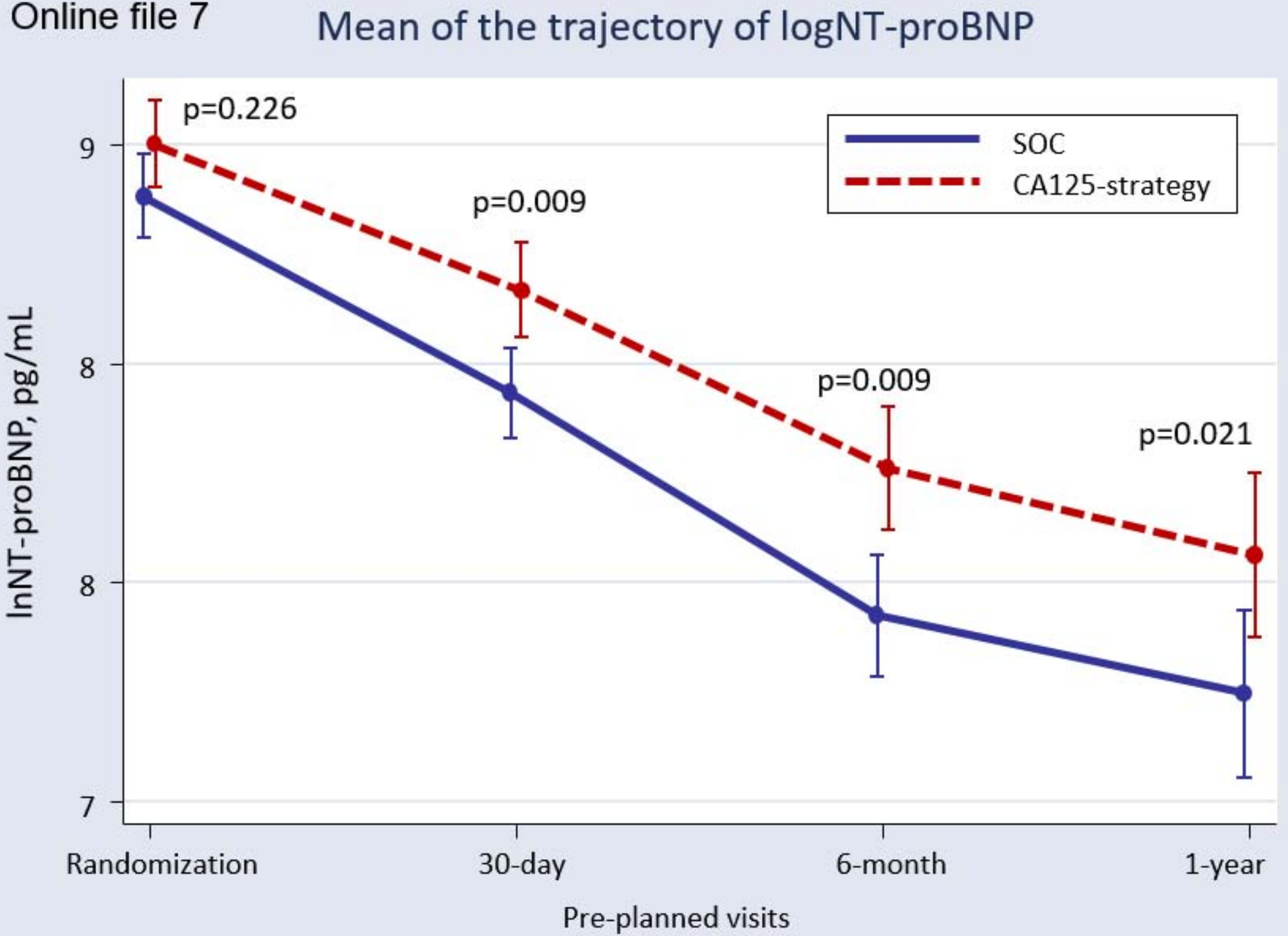


CA125: carbohydrate antigen 125; SOC: standard of care

*Include randomization, preplanned visits, ambulatory visits, and hospitalizations.

SOC: n=816 measurements; CA125-strategy: n=751 measurements

Online file 7



CA125: carbohydrate antigen 125; logNT-proBNP: natural logarhythm of NT-pro-brain natriuretic peptide; SOC: standard of care.