SURVIVAL ANALYSIS AND REPORTING

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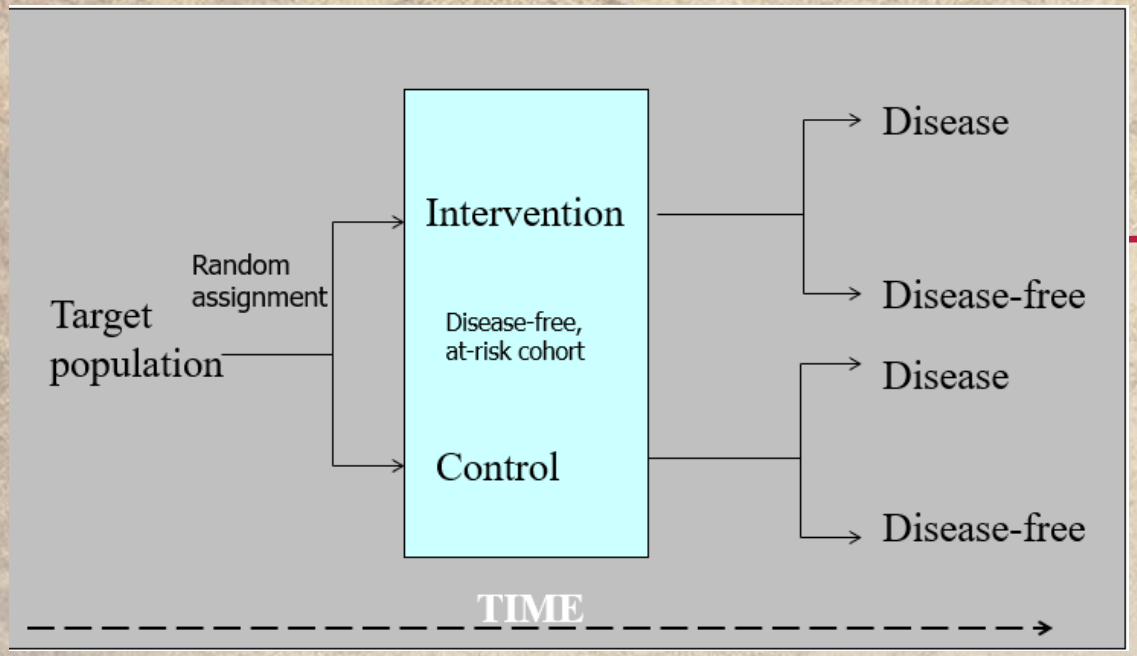
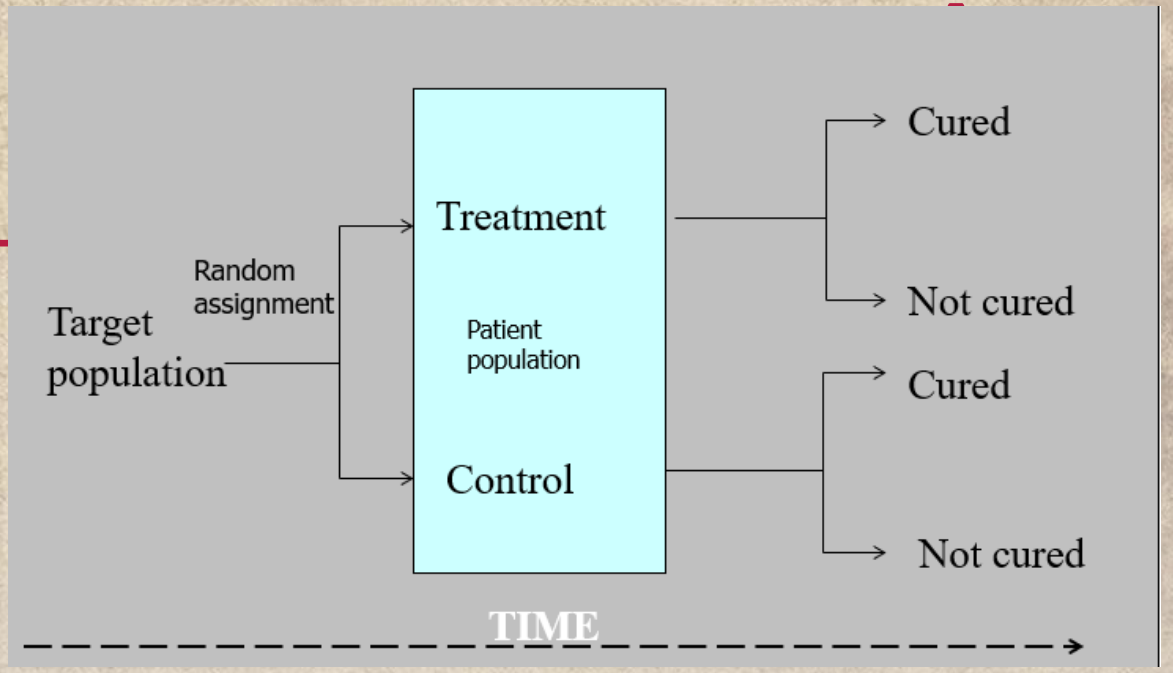
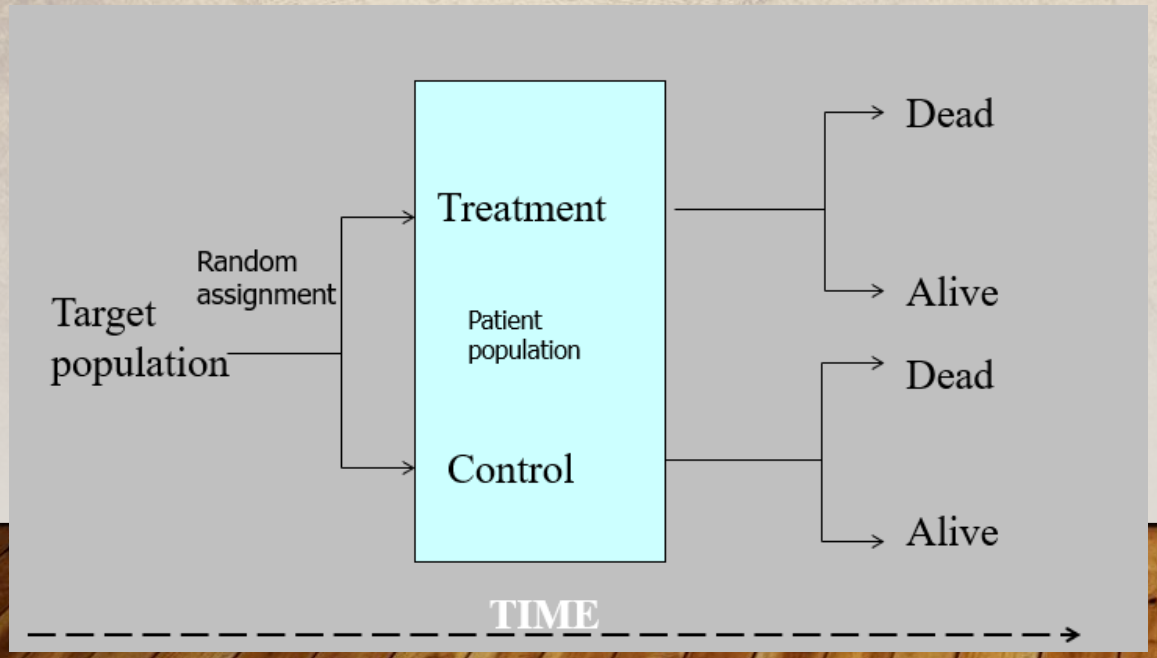
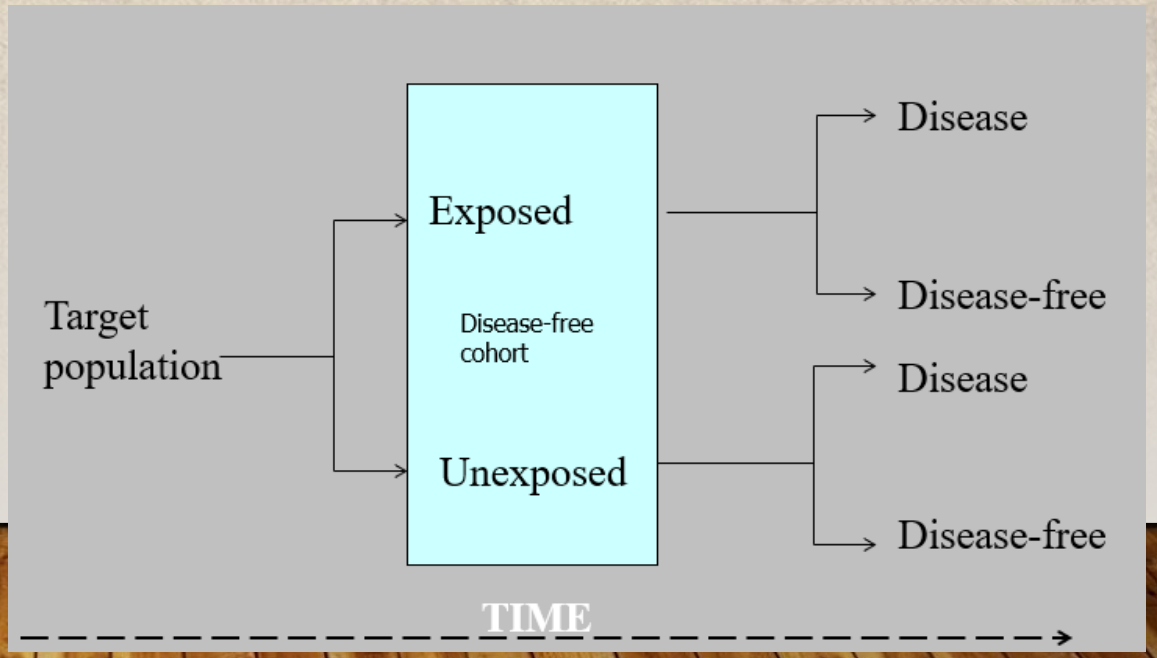
WHAT IS SURVIVAL ANALYSIS

- Statistical methods for analyzing longitudinal data on the occurrence of events
- Events may include death, injury, onset of illness, recovery from illness (binary variables) or transition above or below the clinical threshold of a meaningful continuous variable (e.g. CD4 counts).
- Accommodates data from randomized clinical trial or cohort study design.


Target population
Random assignment
Intervention
Disease-free, at-risk cohort
Control
Disease
Disease-free
Disease
Disease-free
TIME


Target population
Random assignment
Treatment
Patient population
Control
Cured
Not cured
Cured
Not cured
TIME


Target population
Random assignment
Treatment
Patient population
Control
Dead
Alive
Dead
Alive
TIME


Target population
Exposed
Disease-free cohort
Unexposed
Disease
Disease-free
Disease
Disease-free
TIME

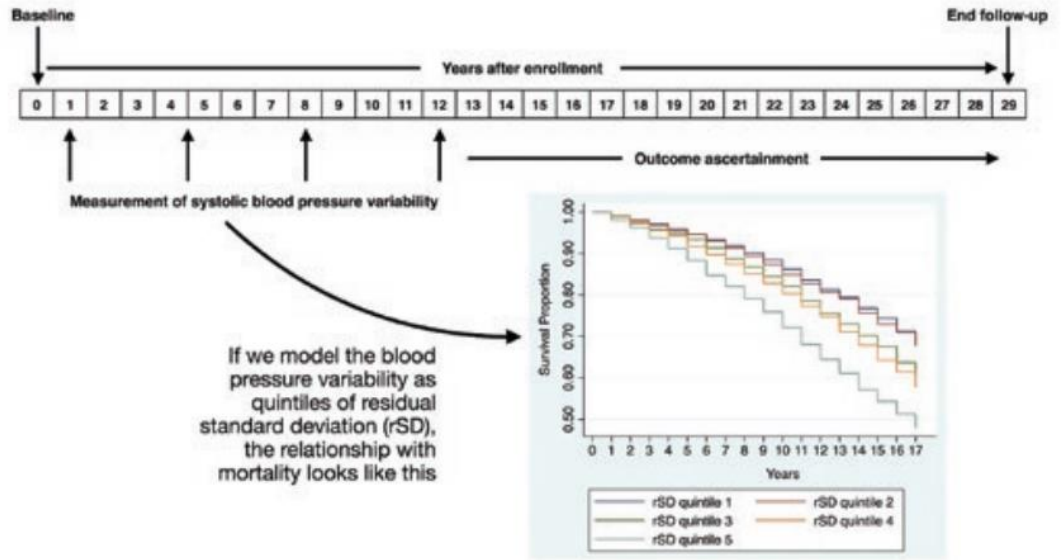
Midlife Blood Pressure Variability and Risk of All-Cause Mortality and Cardiovascular Events During Extended Follow-up

Adam de Havenon, Alen Delic et al.

- BACKGROUND: We aimed to determine the **long-term cardiovascular and mortality effects of BPV in midlife** in participants with and without cardiovascular risk factors.
- METHODS: Long-term BPV was derived utilizing mean systolic blood pressure at Visits 1–4. The primary outcome was mortality from Visit 4 to 2016 and secondary outcome was cardiovascular events. We fit Cox proportional hazards models…
- RESULTS: For every SD higher in systolic residual SD (range 0–60.5 mm Hg, SD = 5.6 mm Hg), the hazard ratio for death was 1.09 (95% confidence interval [CI] 1.05–1.12) and for cardiovascular events was 1.00 (95% CI 0.95–1.05). In cardiovascular disease-free participants (n = 4,452), the corresponding hazard ratio for death was 1.12 (95% CI 1.03–1.21) and for cardiovascular events was 1.01 (95% CI 0.89–1.14).
- We used least absolute shrinkage and selection operator regression analysis to select the final covariates for the adjusted model. We confirmed the proportional hazards assumption of the final Cox model by testing the Schoenfeld residuals and its fit by graphing the Cox–Snell residuals with the Nelson–Aalen cumulative hazard function.

GRAPHICAL ABSTRACT

In 9,578 patients in the Atherosclerosis Risk in the Community Study (ARIC), we found that blood pressure variability was associated with a significantly higher risk of all-cause mortality during a period of up to 17 years of follow-up.



But we did not find that blood pressure variability was associated with cardiovascular events during follow-up.

Closure or Medical Therapy for Cryptogenic Stroke with Patent Foramen Ovale

Anthony J. Furlan, M.D.,
Mark Reisman, M.D.,

Abstract

BACKGROUND

The prevalence of patent foramen ovale among patients with cryptogenic stroke is higher than that in the general population. Closure with a percutaneous device is often recommended in such patients, but it is not known whether this intervention reduces the risk of recurrent stroke.

METHODS

We conducted a multicenter, randomized, open-label trial of closure with a percutaneous device, as compared with medical therapy alone, in patients between 18 and 60 years of age who presented with a cryptogenic stroke or transient ischemic attack (TIA) and had a patent foramen ovale. The primary end point was a composite of stroke or transient ischemic attack during 2 years of follow-up, death from any cause during the first 30 days, or death from neurologic causes between 31 days and 2 years.

RESULTS

A total of 909 patients were enrolled in the trial. The cumulative incidence (Kaplan–Meier estimate) of the primary end point was 5.5% in the closure group (447 patients) as compared with 6.8% in the medical-therapy group (462 patients) (adjusted hazard ratio, 0.78; 95% confidence interval, 0.45 to 1.35; P=0.37). The respective rates were 2.9% and 3.1% for stroke (P=0.79) and 3.1% and 4.1% for TIA (P=0.44). No deaths occurred by 30 days in either group, and there were no deaths from neurologic causes during the 2-year follow-up period. A cause other than paradoxical embolism was usually apparent in patients with recurrent neurologic events.

CONCLUSIONS

In patients with cryptogenic stroke or TIA who had a patent foramen ovale, closure with a device did not offer a greater benefit than medical therapy alone for the prevention of recurrent stroke or TIA. (Funded by NMT Medical; ClinicalTrials.gov number, NCT00201461.)

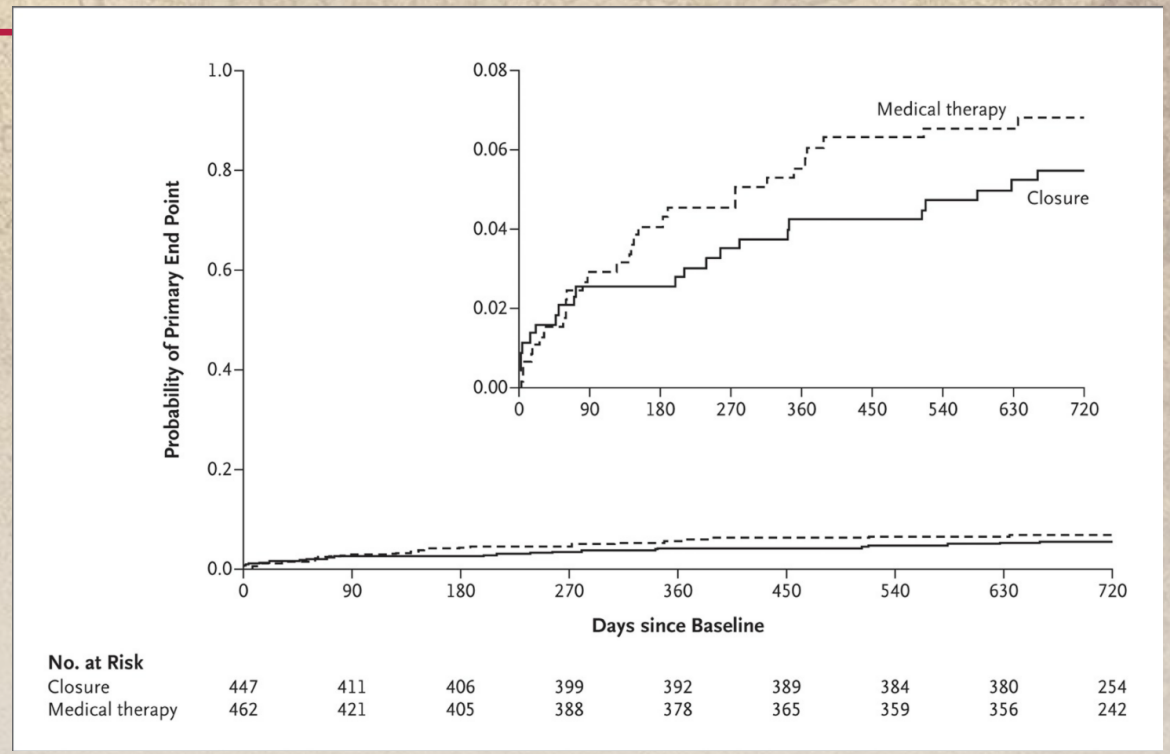


Figure 1. Kaplan–Meier Curve of Time to Primary End Point through 2 Years of Follow-up in the Closure and Medical-Therapy Groups.

OBJECTIVES OF SURVIVAL ANALYSIS

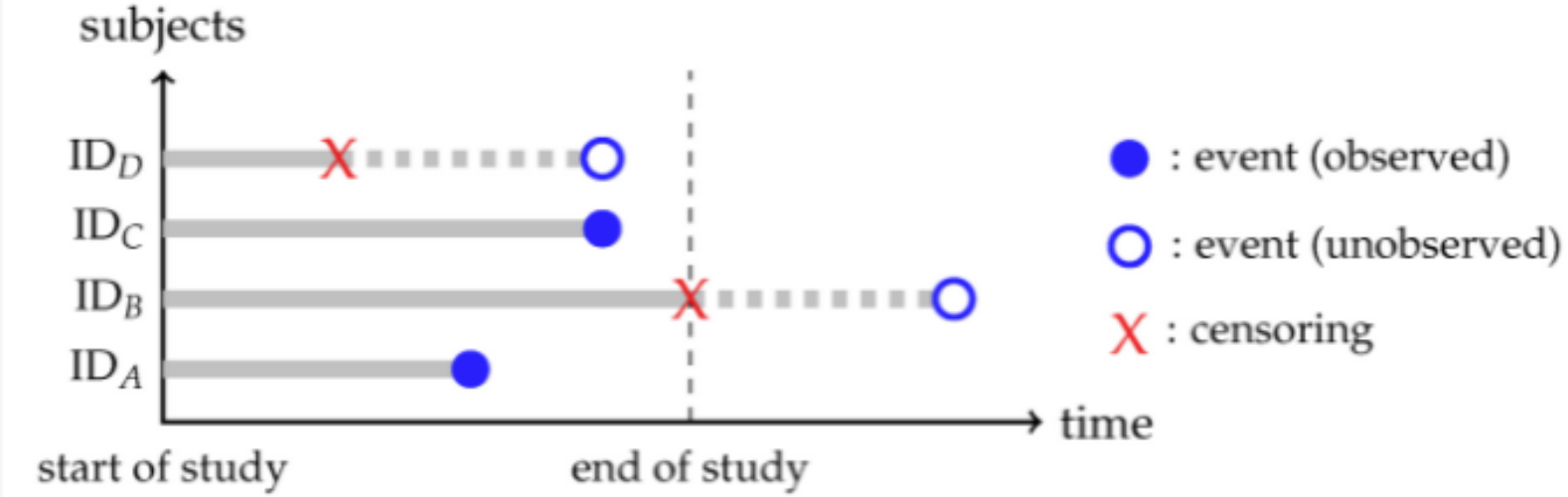
- Estimate time-to-event for a group of individuals, such as time until stroke for a group of patients.
- Compare time-to-event between two or more groups, such as treated vs. placebo patients in an RCT.
- Assess the relationship of co-variables to time-to-event, such as: does weight, age, race, smoking status, etc… affect survival time of patients?

BENEFITS OF SURVIVAL ANALYSIS

- If we analyzed the mean time-to-event using a linear regression/t-test, we would be ignoring a concept called *censoring*
  - Censoring is when a patient is lost to follow up or experiences an event that stops their inclusion in the trial (such as death if the main outcome was stroke)

CENSORING

Figure 1. A visualization for the meaning of right censoring.



HAZARD RATE & SURVIVAL PROBABILITY

- The hazard rate is the probability that an individual will experience an event at time t while that individual is at risk for having an event
  - If the hazard rate is constant over time and it was equal to 1.5 for example this would mean that one would expect 1.5 events to occur in a time interval that is one unit long
- Survival probability is the probability that an individual survives from the time origin to a specified future time
  - Or flip the interpretation and consider failure probability

HAZARD RATE

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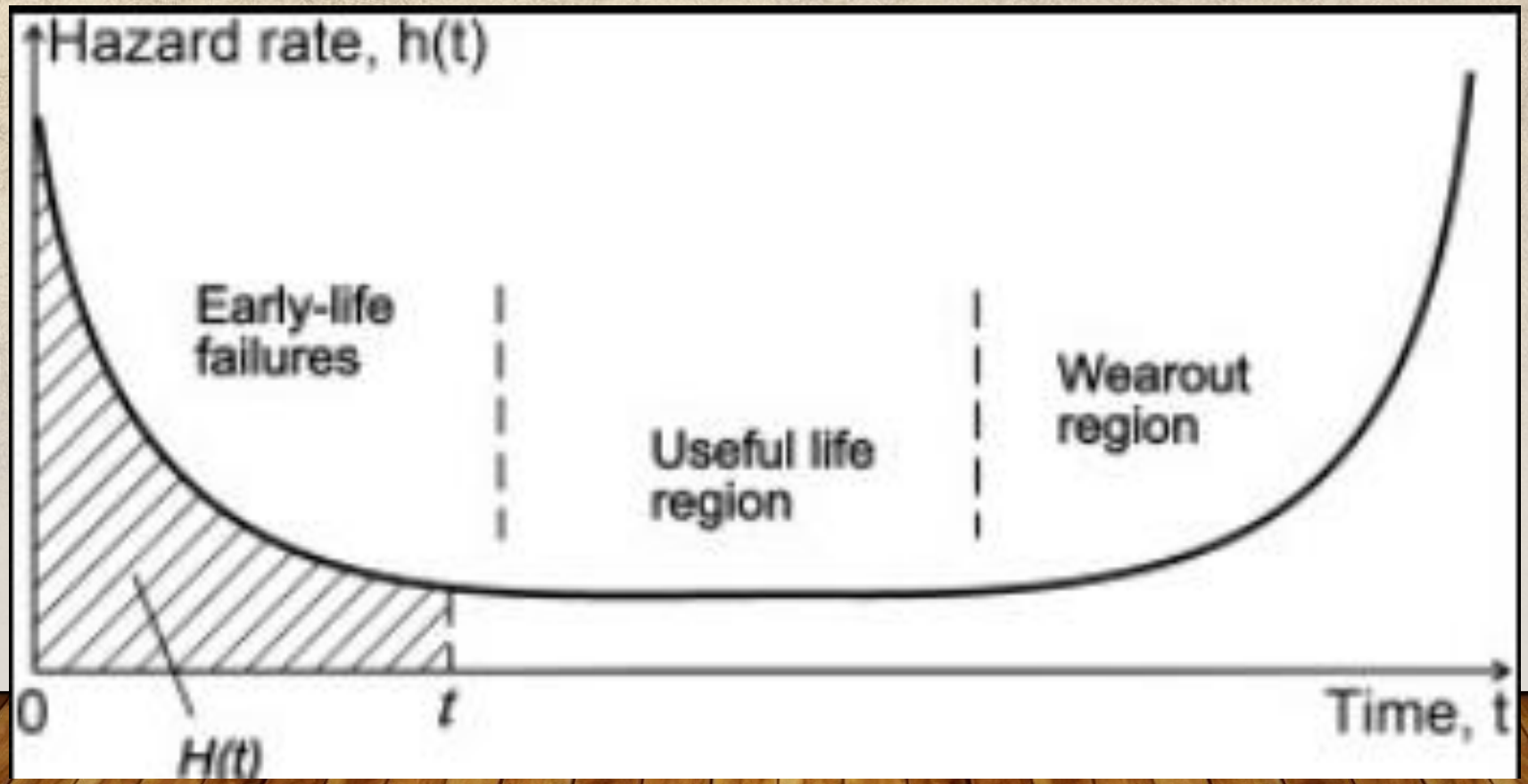
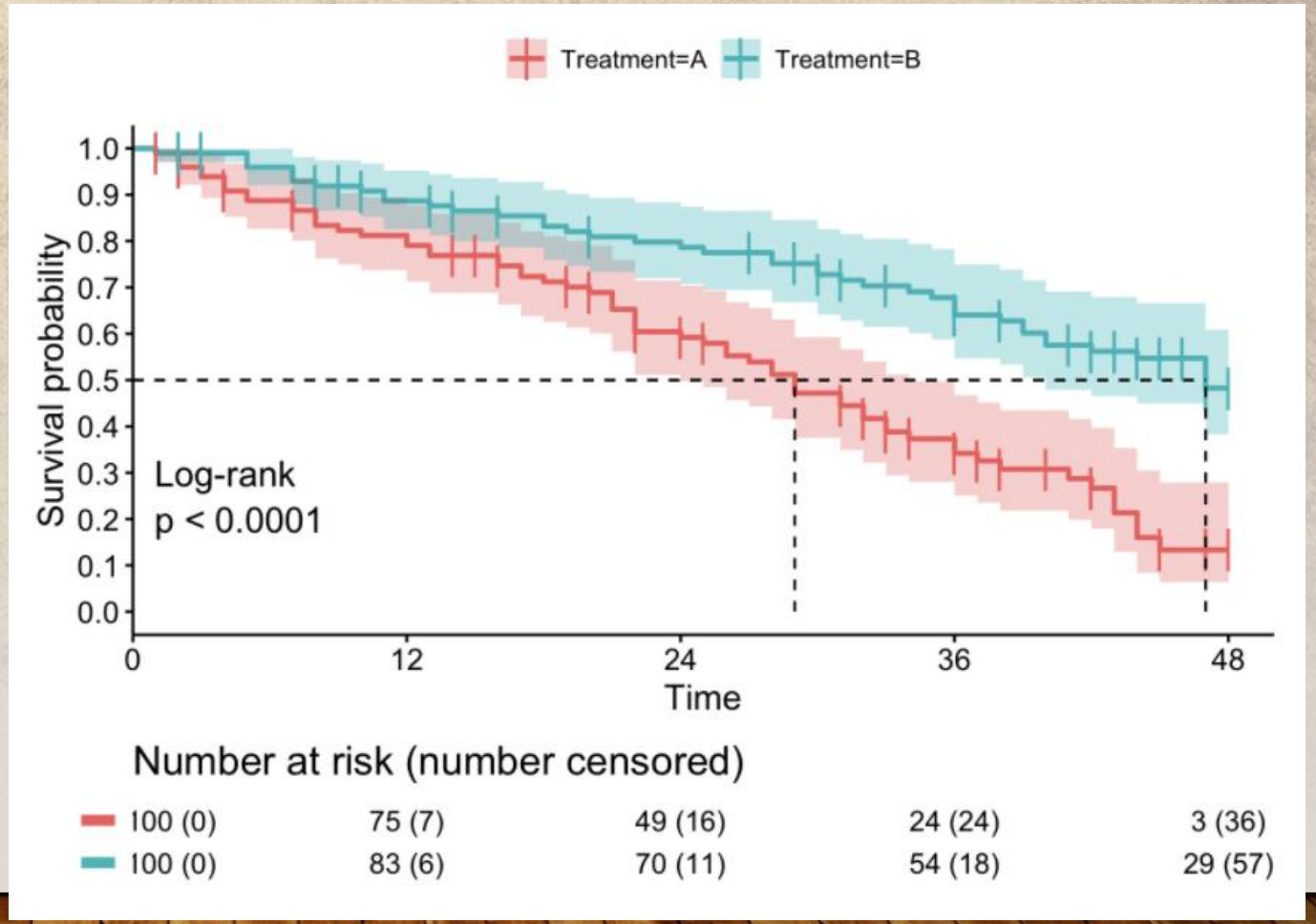


SURVIVAL PROBABILITY & KAPLAN-MEIER PLOT

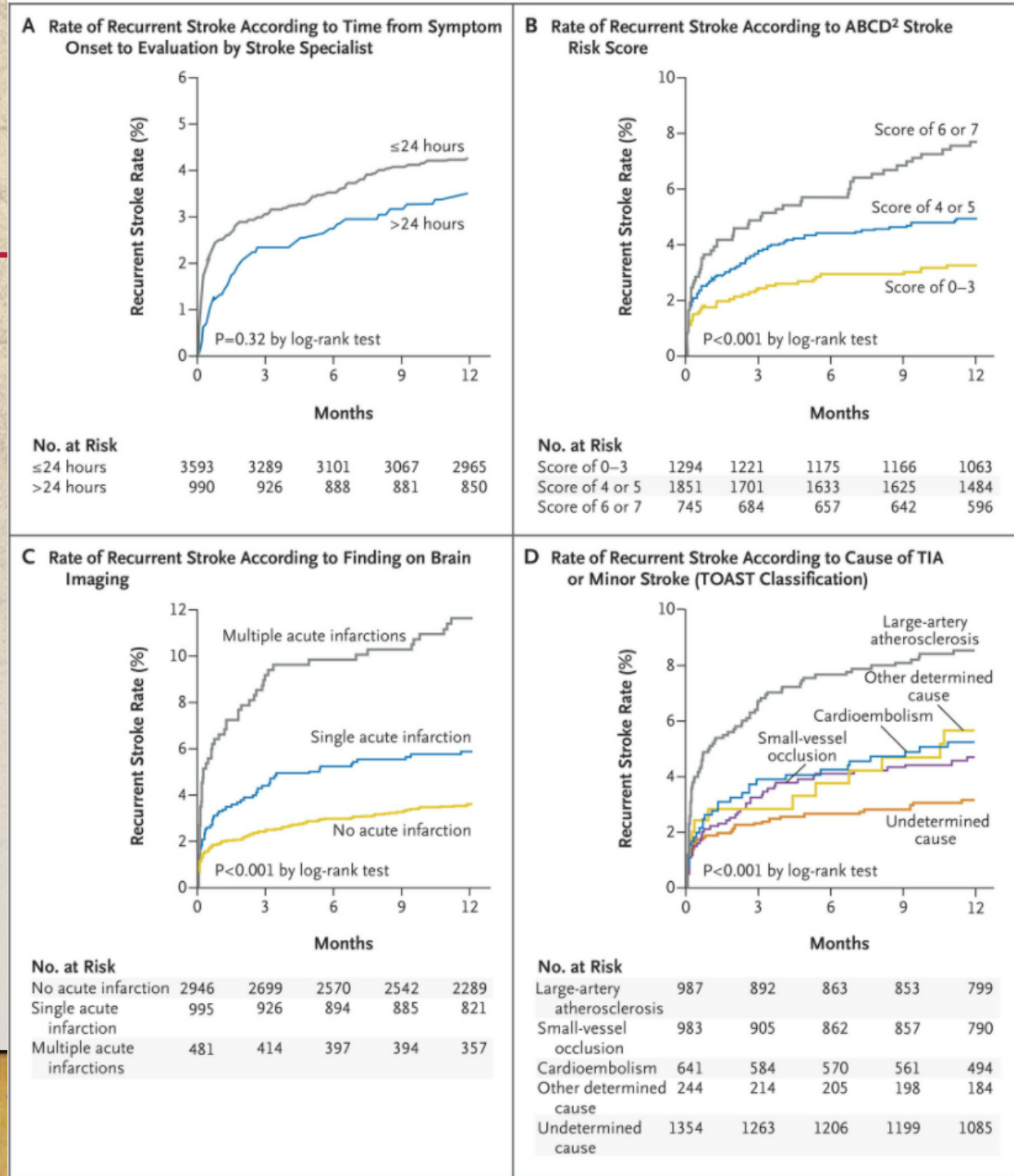
- Can show survival (KP) curves by different groupings (i.e treatment v placebo)
- Can test for significant differences in survival curves using Log-Rank test
  - P-value < 0.05 indicates significant difference at 0.05 alpha level



ONE-YEAR RISK OF STROKE AFTER TRANSIENT ISCHEMIC ATTACK OR MINOR STROKE

Figure 2. Unadjusted Kaplan–Meier Event Curves for Stroke Recurrence from the Time of the Qualifying Event to 1 Year.

Scores on the ABCD^2 stroke risk scale range from 0 to 7, with higher scores indicating a greater risk of stroke; an age of 60 years or older, a blood-pressure level of 140/90 mm Hg or higher, a clinical finding of unilateral weakness or speech impairment, a duration of symptoms of 10 to 59 minutes, and diabetes are each assigned 1 point, and a duration of symptoms of 60 minutes or more is assigned 2 points. The Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification indicates the probable cause of the initial transient ischemic attack (TIA) or stroke; the five main categories are large-artery atherosclerosis, cardioembolism, small-vessel occlusion, other determined cause, and undetermined cause.



HAZARD RATE & COX PROPORTIONAL HAZARDS MODEL

- Regression model used for investigating the association between the survival time of patients and one or more predictor variables.
- KP curves and log-rank test useful for *univariate* models with categorical predictor
  - Good first in data exploration
- Cox model benefits
  - Can fit multiple predictor variables
  - Use both quantitative and qualitative
  - More inference possibilities

HAZARD RATE & COX PROPORTIONAL HAZARDS MODEL

- In Cox models, we are estimating the Hazard Ratio for each covariate of the model
  - HR = 1: No effect
  - HR < 1: Reduction in the hazard
  - HR > 1: Increase in Hazard
- Example: A HR >1 indicates a covariate that is positively associated with the event probability, and thus negatively associated with the length of survival.

SUBCLINICAL ATRIAL FIBRILLATION AND THE RISK OF STROKE

- BACKGROUND: We evaluated whether subclinical episodes of rapid atrial rate detected by implanted devices were **associated with an increased risk of ischemic stroke** in patients who did not have other evidence of atrial fibrillation.
- METHODS: We enrolled 2580 patients, 65 years of age or older, with hypertension and no history of atrial fibrillation, in whom a pacemaker or defibrillator had recently been implanted. We monitored the patients for 3 months and… **followed them for a mean of 2.5 years for the primary outcome of ischemic stroke or systemic embolism**. Patients with pacemakers were **randomly assigned** to receive or not to receive continuous atrial overdrive pacing.
- RESULTS: Subclinical atrial tachyarrhythmias were associated with an increased risk of clinical atrial fibrillation (**hazard ratio, 5.56**; 95% confidence interval [CI], 3.78 to 8.17; P<0.001) and of ischemic stroke or systemic embolism (**hazard ratio, 2.49**; 95% CI, 1.28 to 4.85; P=0.007). Subclinical atrial tachyarrhythmias remained predictive of the primary outcome after adjustment for predictors of stroke (**hazard ratio, 2.50**; 95% CI, 1.28 to 4.89; P=0.008). Continuous atrial overdrive pacing **did not prevent atrial fibrillation**.

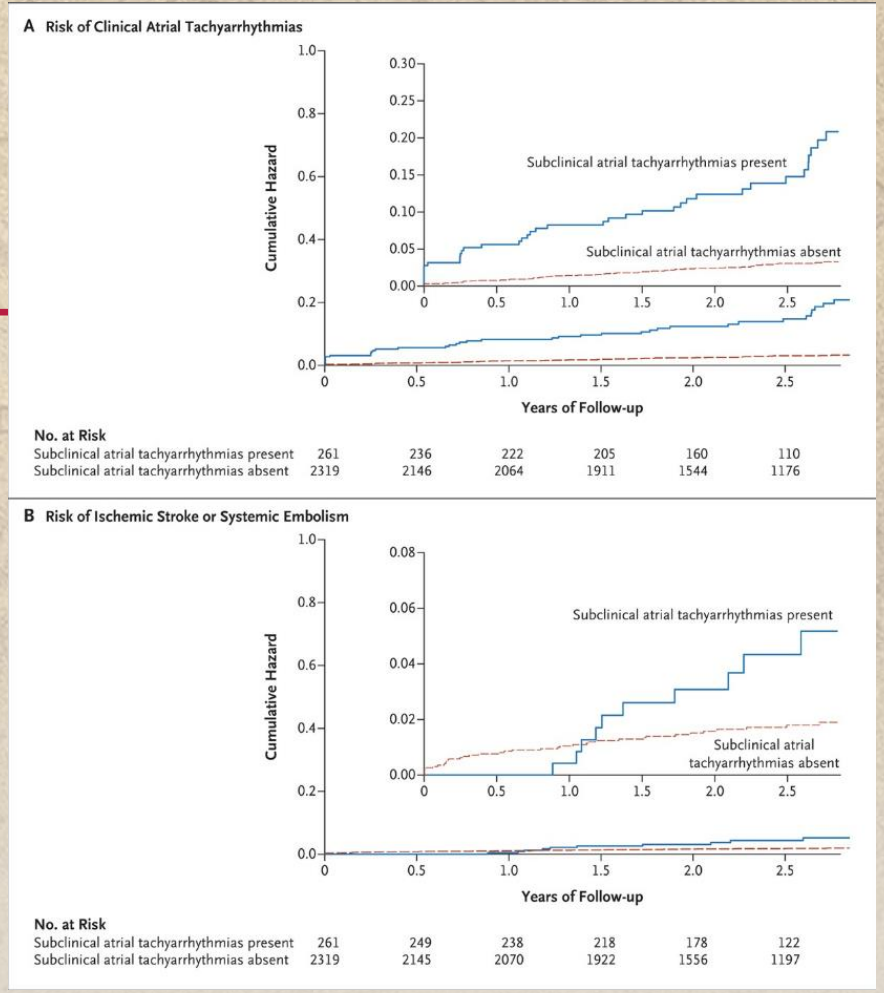


Table 3. Risk of Ischemic Stroke or Systemic Embolism after the 3-Month Visit, According to Baseline $CHADS_2$ Score and According to Whether Subclinical Atrial Tachyarrhythmias Were or Were Not Detected between Enrollment and the 3-Month Visit.

$CHADS_2$ Score	No. of Patients	Subclinical Atrial Tachyarrhythmias between Enrollment and 3 Months						Hazard Ratio for Ischemic Stroke or Systemic Embolism with Subclinical Atrial Tachyarrhythmias (95% CI)*
		Present			Absent			
		no. of patients	*no. of events*	*%/yr*	*no. of patients*	*no. of events*	*%/yr*	
1	600	68	1	0.56	532	4	0.28	2.11 (0.23–18.9)
2	1129	119	4	1.29	1010	18	0.70	1.83 (0.62–5.40)
>2	848	72	6	3.78	776	18	0.97	3.93 (1.55–9.95)

SURVIVAL ANALYSIS MODEL DIAGNOSTICS/ASSUMPTIONS

- One of the main assumptions of the Cox proportional hazard model is proportionality
  - The survival functions are approximately parallel
- This assumption is tested by looking at the Schoenfeld residuals
  - Statistical test: a p-value above 0.05 indicates no evidence that we're violating the assumption
- Can also use Cox-Snell residuals to graphically observe the fit of the model
  - Looking for parallel lines

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Test of proportional-hazards assumption

Time function: Analysis time
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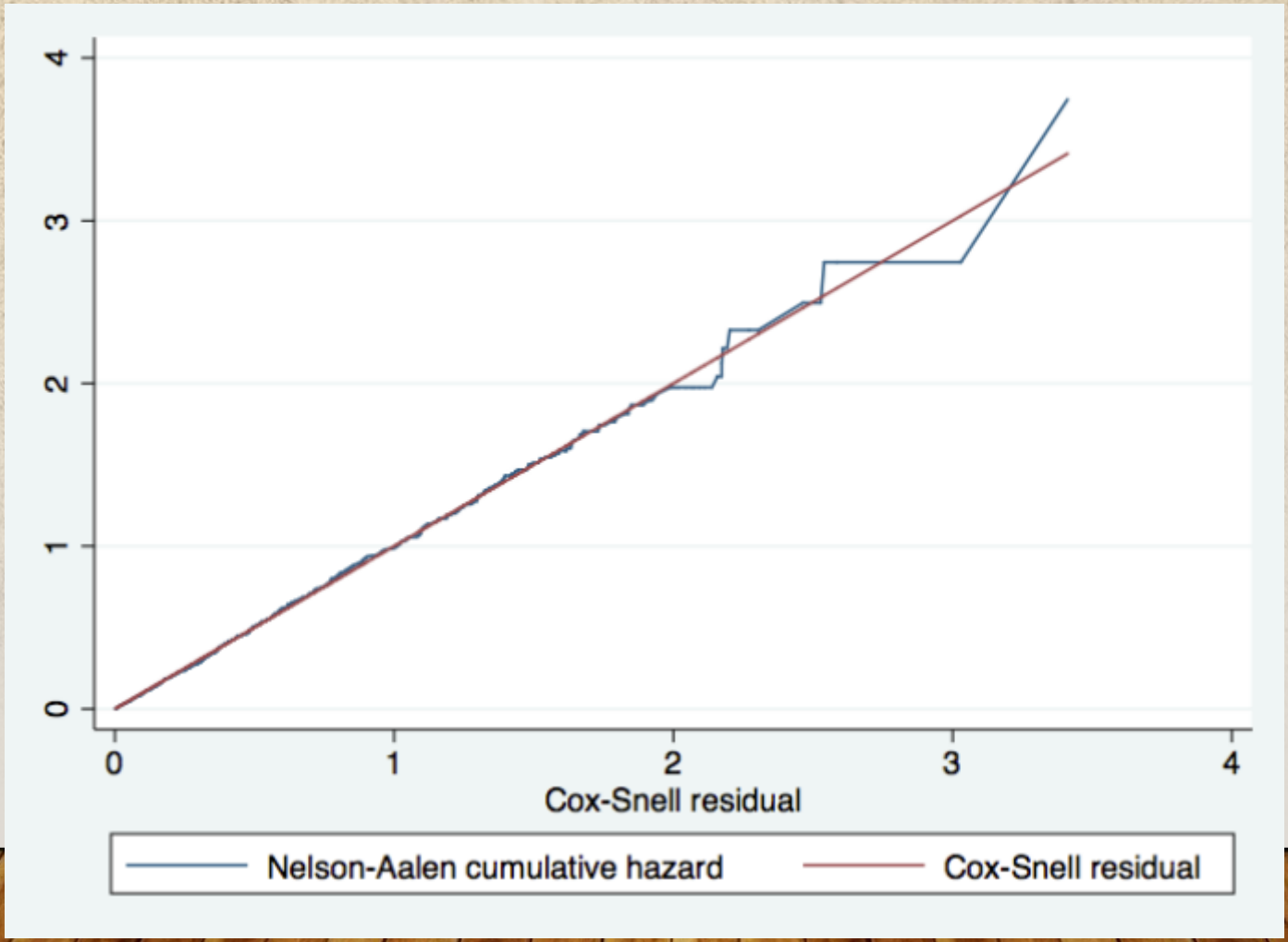
	rho	chi2	df	Prob>chi2
sbp	-0.04375	2.83	1	0.0927
scl	-0.04810	3.54	1	0.0600
age	-0.11937	20.46	1	0.0000
bmi	-0.00276	0.01	1	0.9164
female	0.10301	15.58	1	0.0001
Global test		46.97	5	0.0000

- When proportionality is not met for a variable, you can stratify the model on that variable i.e have one model each for males and females and then aggregate the results

COX SNELL RESIDUALS



Using Ultrasound and Inflammation to Improve Prediction of Ischemic Stroke: A Secondary Analysis of the Multi-Ethnic Study of Atherosclerosis

Hediyeh Baradaran
Alen Delic
Adam de Havenon

- *Background*. We examined the relationship between baseline ultrasound and inflammation measurements and subsequent primary ischemic stroke risk.
- *Methods*. Multi-Ethnic Study of Atherosclerosis (MESA) was used. primary outcome is the incident ischemic stroke during follow-up. The predictor variables are 9 carotid ultrasound-derived measurements and 6 serum inflammation measurements from the baseline study visit. We fit Cox regression models to the outcome of ischemic stroke.
- In the Cox models, we found that carotid distensibility (CD), carotid stenosis (CS), and serum interleukin-6 (IL-6) were associated with incident stroke. Adding tertiles of CD, IL-6, and categories of CS to a baseline model that included traditional clinical vascular risk factors resulted in a better model fit than traditional risk factors alone as indicated by goodness-of-fit statistics (AIC, NRI, IDI)
- Net reclassification improvement (NRI) and integrated discrimination improvement (IDI) were used to assess improvement in prediction with addition predictors. Goodness-of-fit of the baseline and new model was assessed by evaluating results from a likelihood ratio test and AIC

Effect of adding individual serum inflammatory marker variables to the baseline Cox proportional hazards model

Serum inflammatory marker	Hazard ratio[1]	95% CI	*p* value
CRP	1.01	0.98–1.04	0.433
Fibrinogen antigen (mg/dL)	1.00	1.00–1.00	0.192
Plasmin-antiplasmin complex (nM)	1.03	0.97–1.10	0.324
D-Dimer (μg/mL)	0.95	0.71–1.26	0.704
Factor VIII (%)	1.00	1.00–1.01	0.608
IL-6 (pg/mL)	*1.21*	*1.08–1.36*	*0.001*

Italicized variables are statistically significant. CRP, C-reactive protein.

[1]Adjusted for baseline age, diabetes, hypertension, total cholesterol, smoking, and systolic blood pressure ≥160 mm Hg.