

Methods: Mind the Gap

Webinar Series

Restricted Mean Survival Time Approaches for Time-to-Event Outcomes in Prevention Research

Presented by:

Hajime Uno, Ph.D.
Harvard Medical School



National Institutes of Health
Office of Disease Prevention

NIH Office of Disease Prevention
Methods: Mind the Gap Webinar Series

Restricted Mean Survival Time Approaches for Time-to-Event Outcomes in Prevention Research

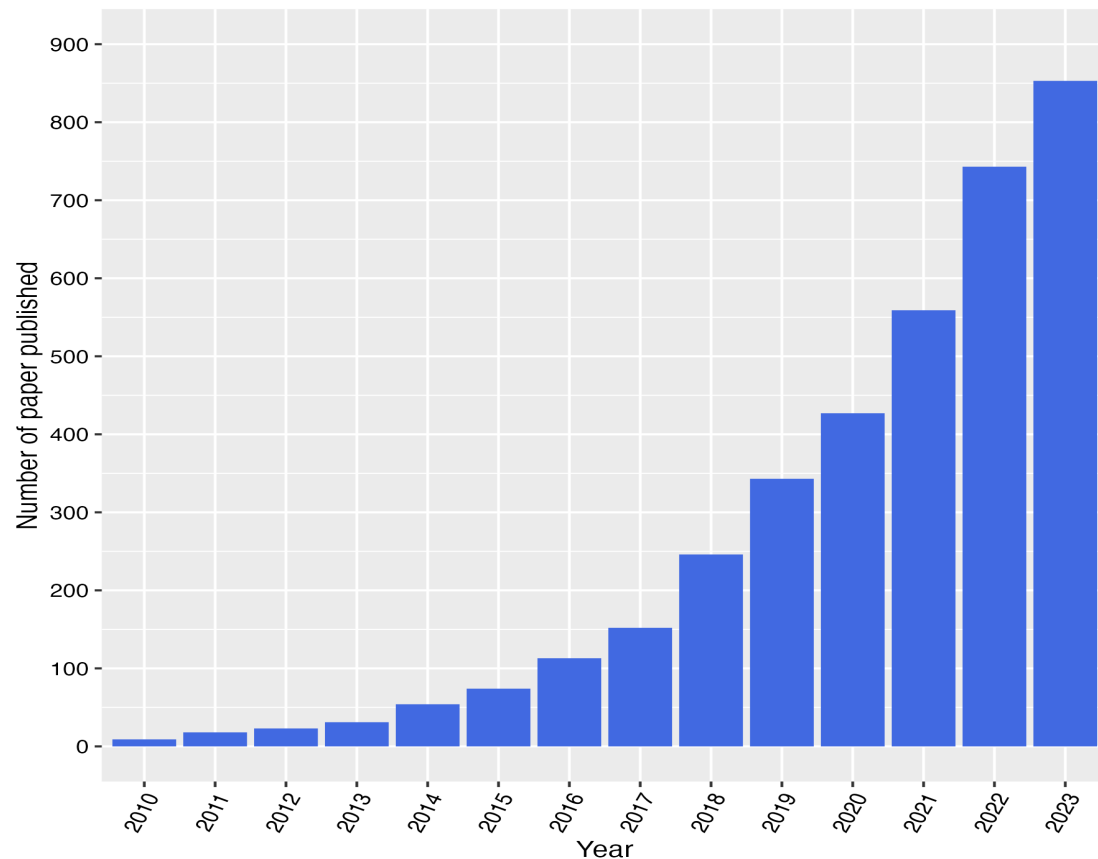
Hajime Uno, PhD

Dana-Farber Cancer Institute/Harvard Medical School

RMST is getting popular...

RMST was proposed
by Irwin (1947)

Karrison
(1997, Cont.Clin.Trial)



Outline of the presentation

1. Foundation of RMST
 - Definition and Interpretation
 - Inference procedure
2. Why is the RMST gaining attention?
3. Applications of RMST approaches in prevention research
4. Regression analysis for RMST
5. Practical implementation of RMST analysis using software packages
6. Summary

1. Foundation of RMST

Restricted Mean Survival Time (RMST)

Irwin 1949

Let $T (> 0)$ be the event time, and let $S(t)$ be the survival function of T

Mean Survival Time: $E(T) = \int_0^{\infty} S(u)du$

Mean value is an intuitive summary of the event time distribution.

However, in practice, it is hard to wait until we observe the event times for all study participants. Therefore, the MST would not be always estimable.

Instead of T , we consider a truncated event time, $\min(T, \tau)$

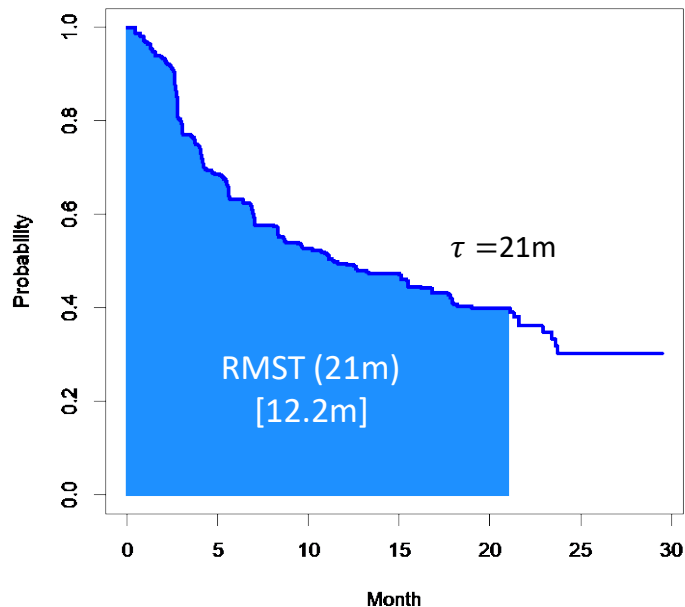
Restricted Mean Survival Time: $E\{\min(T, \tau)\} = \int_0^{\tau} S(u)du$

Interpretation of RMST: $E\{\min(T, \tau)\} = \int_0^\tau S(u)du$

1. The mean survival time that individuals in a study population survive up to τ
2. Expected event-free time in τ –year (or τ – month) follow-up

→ RMST is an intuitive summary measure for patients and clinicians

Example: $\tau = 21\text{m}$



On average, subjects are alive (or event-free) for 12.2 months in 21m of follow-up

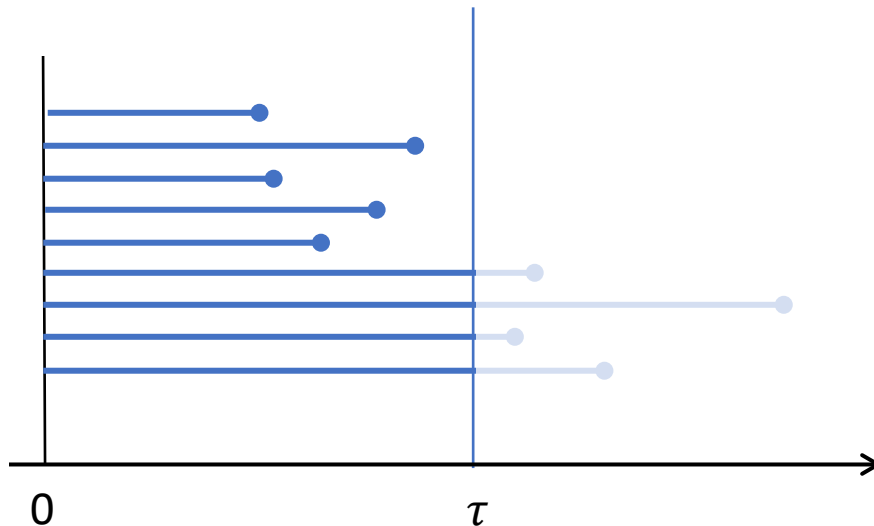
Inference of RMST: $\mu(\tau) = E\{\min(T, \tau)\} = \int_0^\tau S(u)du$

If there are no censored observations

Observed data: $\{T_1, T_2, \dots, T_n\}$

Average

$$\hat{\mu}(\tau) = n^{-1} \sum_{i=1}^n \min(T_i, \tau)$$



$$\text{Inference of RMST: } \mu(\tau) = E\{\min(T, \tau)\} = \int_0^\tau S(u)du$$

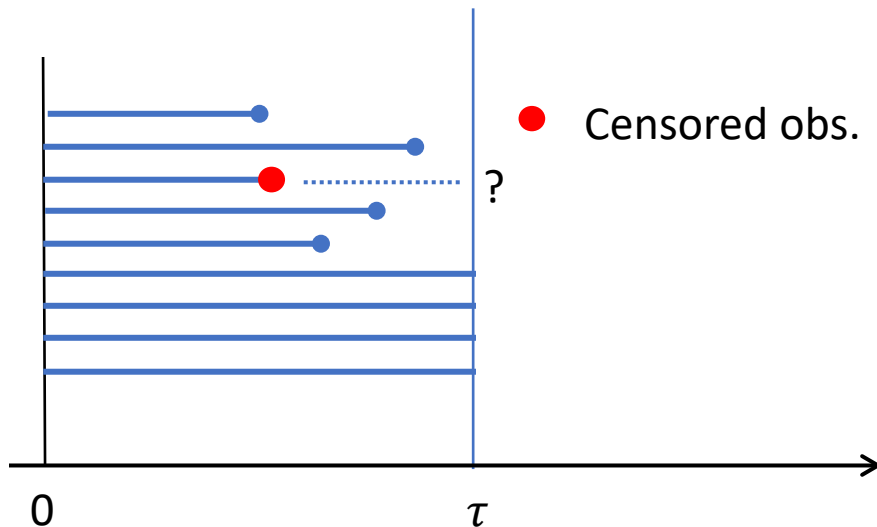
If there are no censored observations

Observed data: $\{T_1, T_2, \dots, T_n\}$

Average

$$\hat{\mu}(\tau) = n^{-1} \sum_{i=1}^n \min(T_i, \tau)$$

However, this estimator does not always work, because we usually have censored observations in practice.



Inference of RMST: $\mu(\tau) = E\{\min(T, \tau)\} = \int_0^\tau S(u)du$

Non-parametric inference

$\hat{S}(t)$: Kaplan-Meier estimator for $S(t)$ $\Rightarrow$ $\hat{\mu}(\tau) = \int_0^\tau \hat{S}(u)du$

Consistency: $\hat{\mu}(\tau) \rightarrow \mu(\tau)$ in prob.

Asymptotic Normality: $W(\tau) = n^{1/2} \left\{ \int_0^\tau \hat{S}(t)dt - \int_0^\tau S(t)dt \right\} \rightarrow N(0, V)$ in dist.

$$V = \int_0^\tau \left[\int_t^\tau S(u)du \right]^2 \frac{d\Lambda(t)}{\pi_X(t)}$$

$\Lambda(t)$: Cum. haz. fun. for the even time T
 $\pi_X(t) : P\{\min(T, C) \geq t\}$
 C : censoring time

Thus, $\hat{\mu}(\tau)$ approximately follows $N(\mu(\tau), V/n)$

0.95 asymptotic CI for $\mu(\tau)$: $\left[\hat{\mu}(\tau) - \frac{1.96\hat{V}}{n}, \hat{\mu}(\tau) + \frac{1.96\hat{V}}{n} \right]$

Inference of RMST: $\mu(\tau) = E\{\min(T, \tau)\} = \int_0^\tau S(u)du$

Parametric inference

Assume the event time T follows a parametric distribution
(e.g., a Weibull distribution with two parameters (shape: k , scale λ))

Estimate the parameters from the observed data using the maximum likelihood (ML) method and derive the estimated survival curve

$$\hat{S}(t; \hat{k}, \hat{\lambda}): \text{Estimator for } S(t; k, \lambda) \rightarrow \hat{\mu}(\tau) = \int_0^\tau \hat{S}(u; \hat{k}, \hat{\lambda}) du$$

Consistency and asymptotic normality directly follows from the ML theories

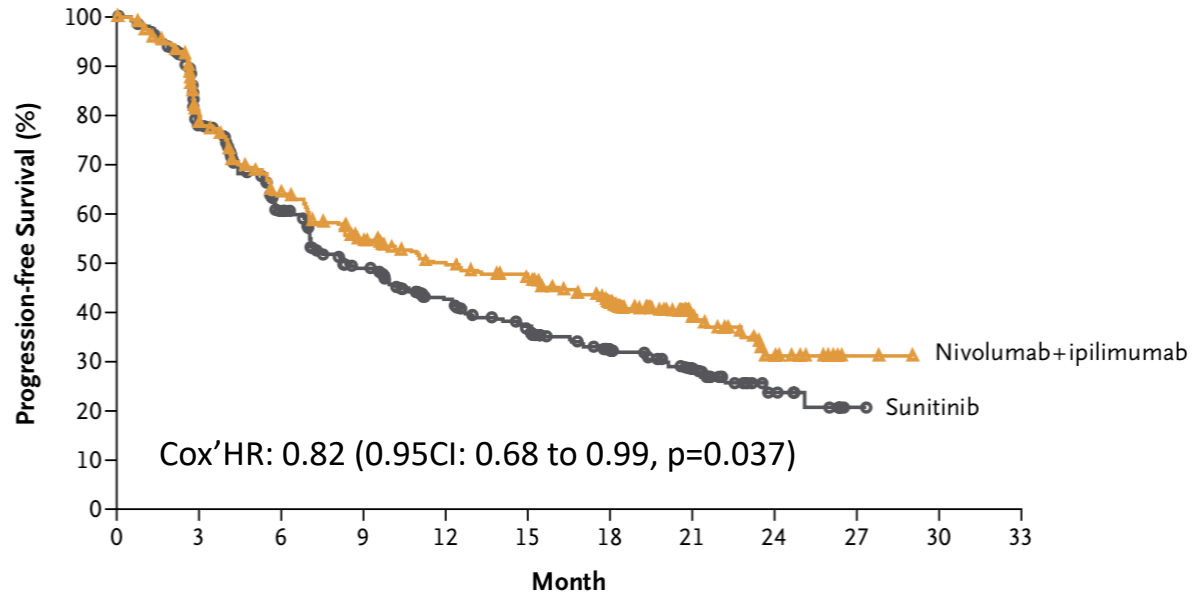
Example of the RMST analysis for two-sample comparison in a randomized clinical trial (CheckMate 214 Study)



Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma

R.J. Motzer, N.M. Tannir, D.F. McDermott, O. Arén Frontera, B. Melichar, T.K. Choueiri, E.R. Plimack, P. Barthélémy, C. Porta, S. George, T. Powles, F. Donskov, V. Neiman, C.K. Kollmannsberger, P. Salman, H. Gurney, R. Hawkins, A. Ravaud, M.-O. Grimm, S. Bracarda, C.H. Barrios, Y. Tomita, D. Castellano, B.I. Rini, A.C. Chen, S. Mekan, M.B. McHenry, M. Wind-Rotolo, J. Doan, P. Sharma, H.J. Hammers, and B. Escudier, for the CheckMate 214 Investigators*

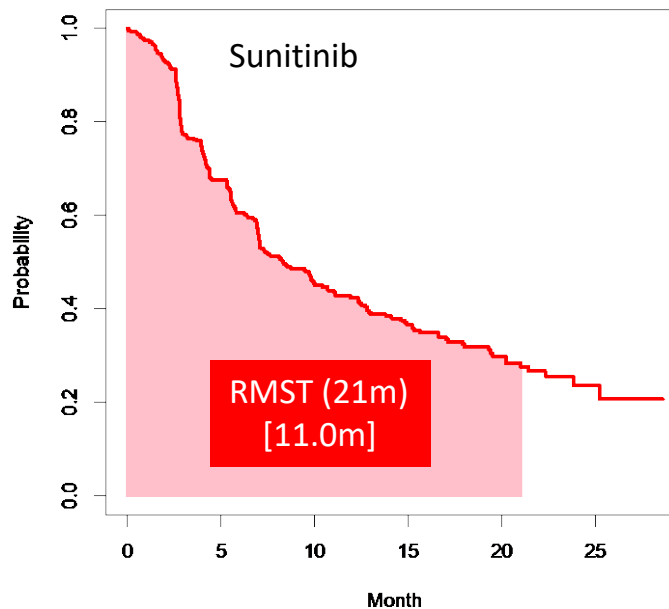
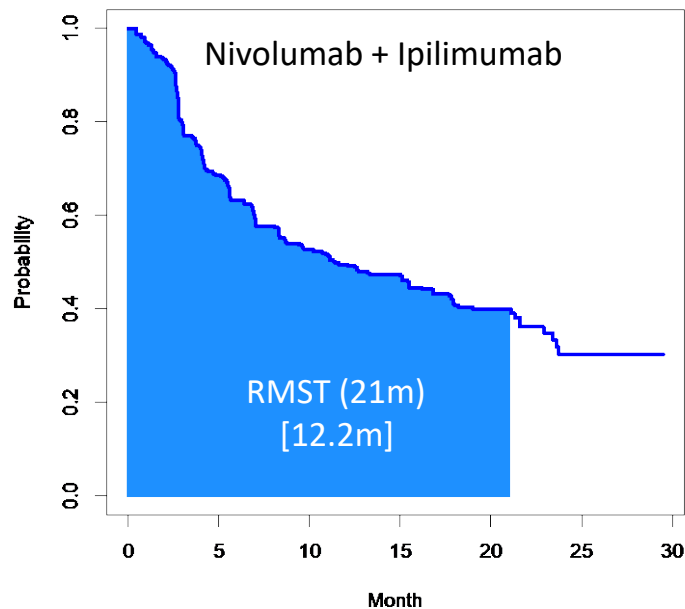
CheckMate 214: Progression-Free Survival



No. at Risk

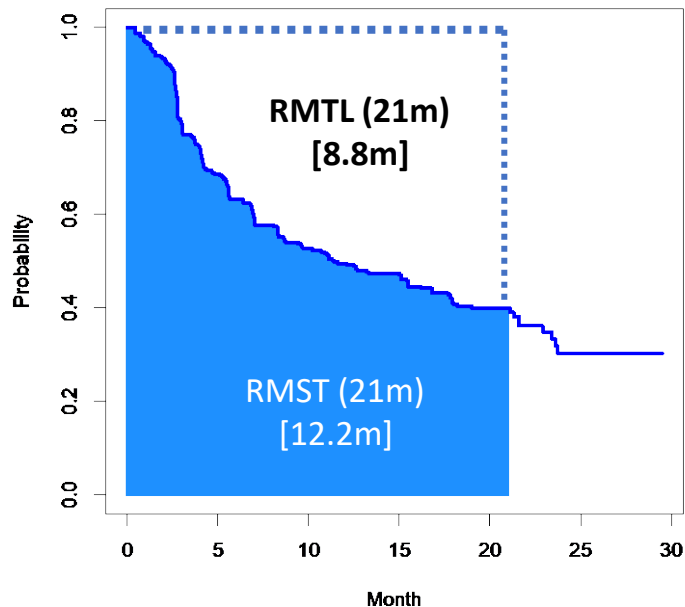
Nivolumab+ipilimumab	425	304	233	187	163	149	118	46	17	3	0
Sunitinib	422	282	191	139	107	86	57	33	11	1	0

Ex. Between-Group Comparison with RMST in RCT setting



Nivolumab +Ipilimumab vs. Sunitinib	Estimate	0.95 CI	p-value
Difference	1.2m	0.5m to 2.4m	0.041
Ratio	1.1	1.0 to 1.2	0.040

A related measure: Restricted Mean Time Lost (RMTL)



$$\begin{aligned}\tau - E\{\min(T, \tau)\} &= \tau - \int_0^{\tau} S(u) du \\ &= \int_0^{\tau} \{1 - S(u)\} du\end{aligned}$$

Interpretation

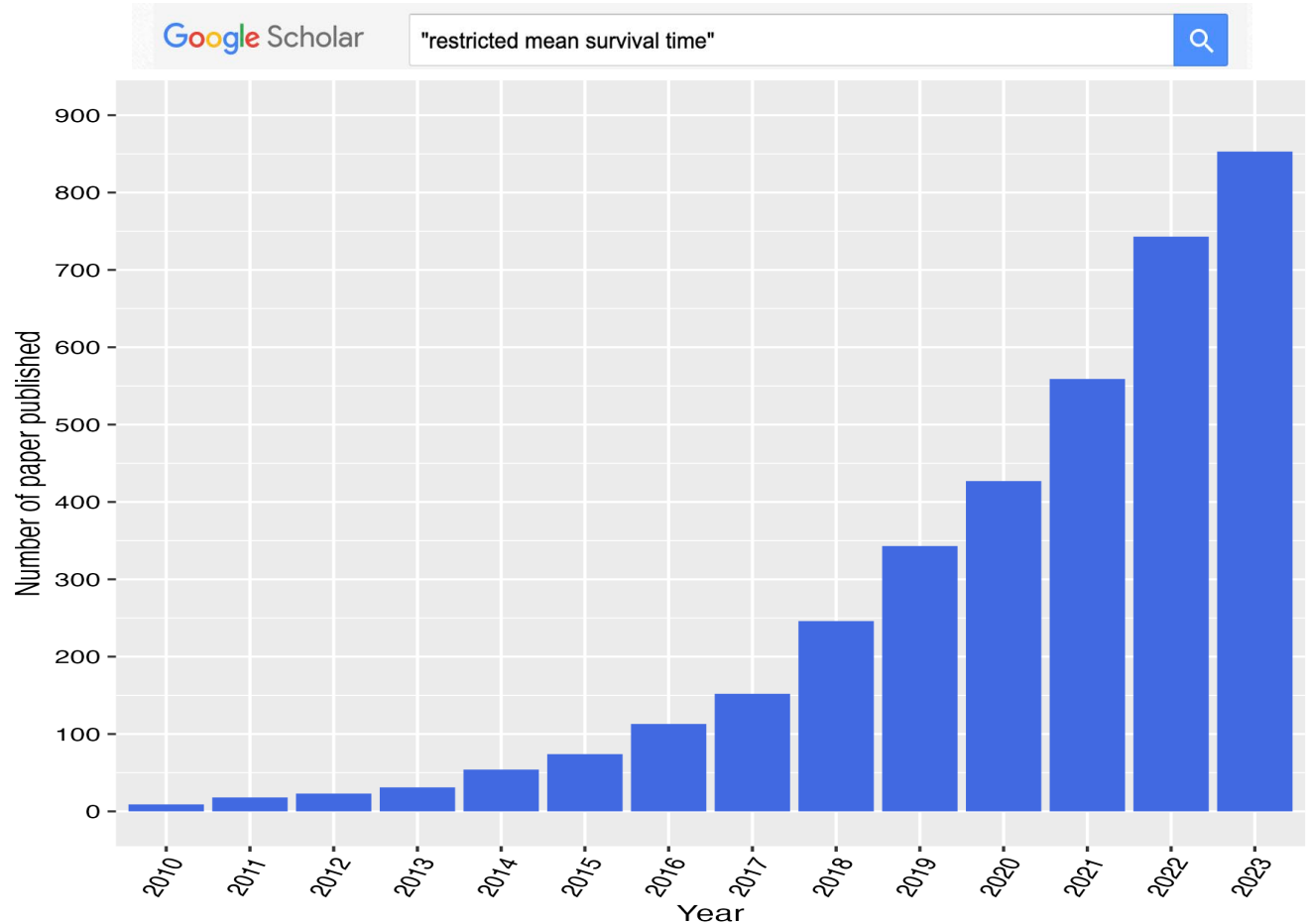
- Average time lost during the follow-up from 0 to τ

Example (see the left fig.)

- On average, we lose 8.8m
- On average, subjects are not in the event free for 8.8 months during 21-months follow-up.

2. Why is the RMST approach gaining attention?

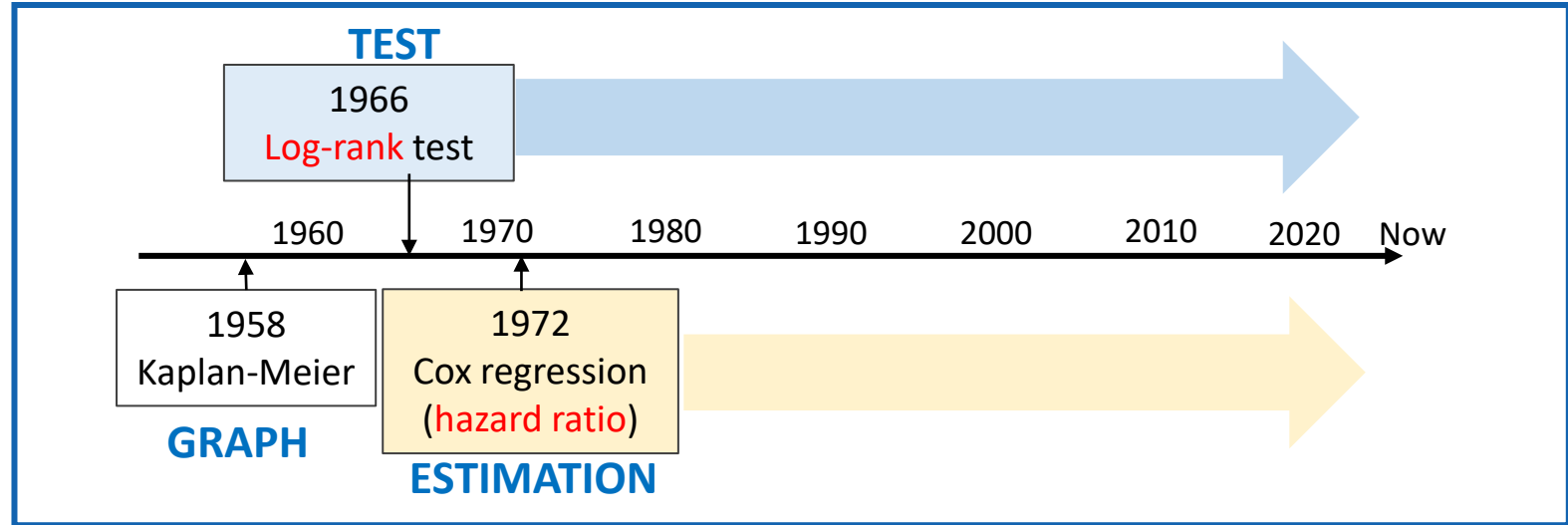
Why is RMST getting popular?



RMST was proposed
by Irwin (1947)

Karrison
(1997, Cont.Clin.Trial)

Established methods for time-to-event data in comparative studies



95% of recent cancer RCTs reported in high-profile journals in 2016-2017 used the combination of log-rank test and hazard ratio estimation.
(Uno et al. 2020, *The Oncologist*)

Significant advantages of Sir Prof. David Cox's HR approach

- Test/Estimation coherency
 - Tests based on HR are asymptotically equivalent to the logrank test
- Offers the most powerful test to detect proportional hazard differences
- Efficient
 - It does not have to estimate “hazard” for each treatment group separately to determine the HR.
 - It can focus inference on a single metric (ie, HR) that quantifies difference between two survival curves, making others nuisance parameters.
- Supported by rigorous and elegant theories
- Great experience (history) in clinical research community
- Accessibility (software, instructions)



Q: Despite these advantages of the traditional HR-approach, why is RMST attracting so much attention?

The traditional HR-approach has significant limitations in providing quantitative information about the magnitude of intervention effect

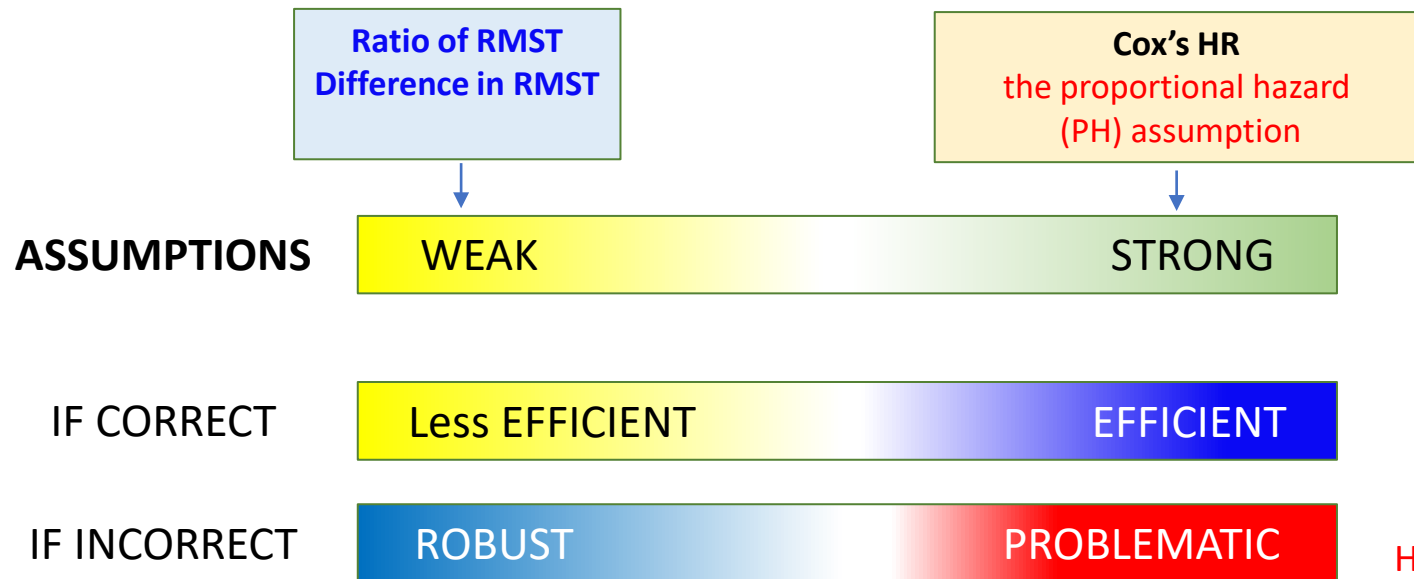
Traditional HR-based approach versus RMST-based approach

References

- *Uno et al. (JCO 2014)*
- *Uno et al (Annals of Intern Med 2015)*
- *Horiguchi, Hassett, Uno (Oncologist 2019)*

Traditional HR-based vs. RMST-based approach

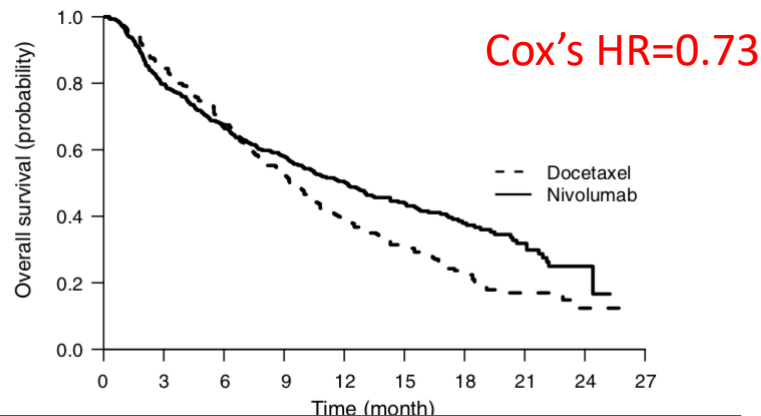
(1) Assumptions



HR depends on study-specific censoring time distribution

Why does HR depend on censoring distribution under non-PH?

Survival functions

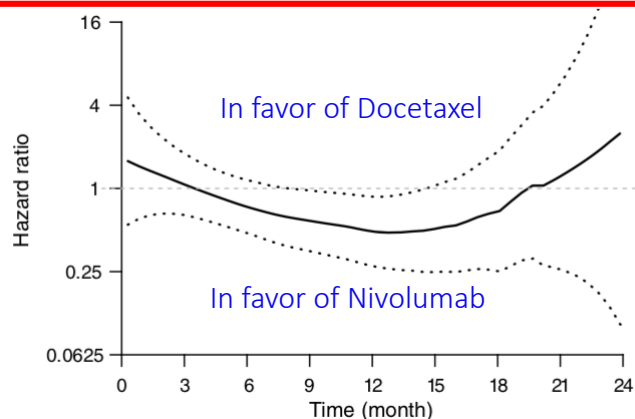


at risk

Nivolumab	292	232	194	169	146	123	62	32	9	0
Docetaxel	290	244	194	150	111	87	34	10	5	0

The size of risk sets gets smaller
- when subjects have events
- also when they are “censored”

Time-specific
hazard ratio (solid line)



Censoring time is affected by patient enrollment period and follow-up periods, **which are study-specific.**

Traditional HR-based vs. RMST-based approach

(2) Approach for estimating the between-group contrast

	Ratio of RMST Difference in RMST	Cox's HR (the PH assumption)
Approach	Estimate RMSTs for two groups and take difference or ratio	Directly estimate the between-group contrast (HR)
Efficiency	Less eff.	More eff.
Clinical Interpretation	Easy	Difficult

HR cannot address a practically important recommendation

HR cannot address a practically important recommendation

References:

- CONSORT Guideline 2010
- Annual of Internal Medicine. Guidance for Authors

CONSORT Statement (re binary outcomes)

Annals of Internal Medicine

ACADEMIA AND CLINIC

CONSORT 2010 Statement: Updated Guidelines for Reporting Parallel Group Randomized Trials

Kenneth F. Schulz, PhD, MBA; Douglas G. Altman, DSc; and David Moher, PhD for the CONSORT Group*

The CONSORT (Consolidated Standards of Reporting Trials) statement is used worldwide to improve the reporting of randomized, controlled trials. Schulz and colleagues describe the latest version, CONSORT 2010, which updates the reporting guideline based on new methodological evidence and accumulating experience.

Ann Intern Med. 2010;152.

www.annals.org

For author affiliations, see end of text.

* For the CONSORT Group contributors to CONSORT 2010, see the Appendix, available at www.annals.org.

This article was published at www.annals.org on 24 March 2010.

CONSORT 2010 Checklist of Information to Include When Reporting a Randomized Trial*

Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended

*Why do we need both absolute difference and ratio?
(Example of binary outcomes)*

	Adv. Event (Case 1)	Adv. Event (Case 2)
Ratio	2.0	2.0
Difference	20%	0.001%
Treatment group	40%	0.002%
Control group	20%	0.001%

- We need two numbers to assess if the estimated treatment effect magnitude is clinically meaningfully large or not
- This applies to time-to-event outcomes as well as binary outcomes

Hazard Ratios and Standardized Cumulative Incidence

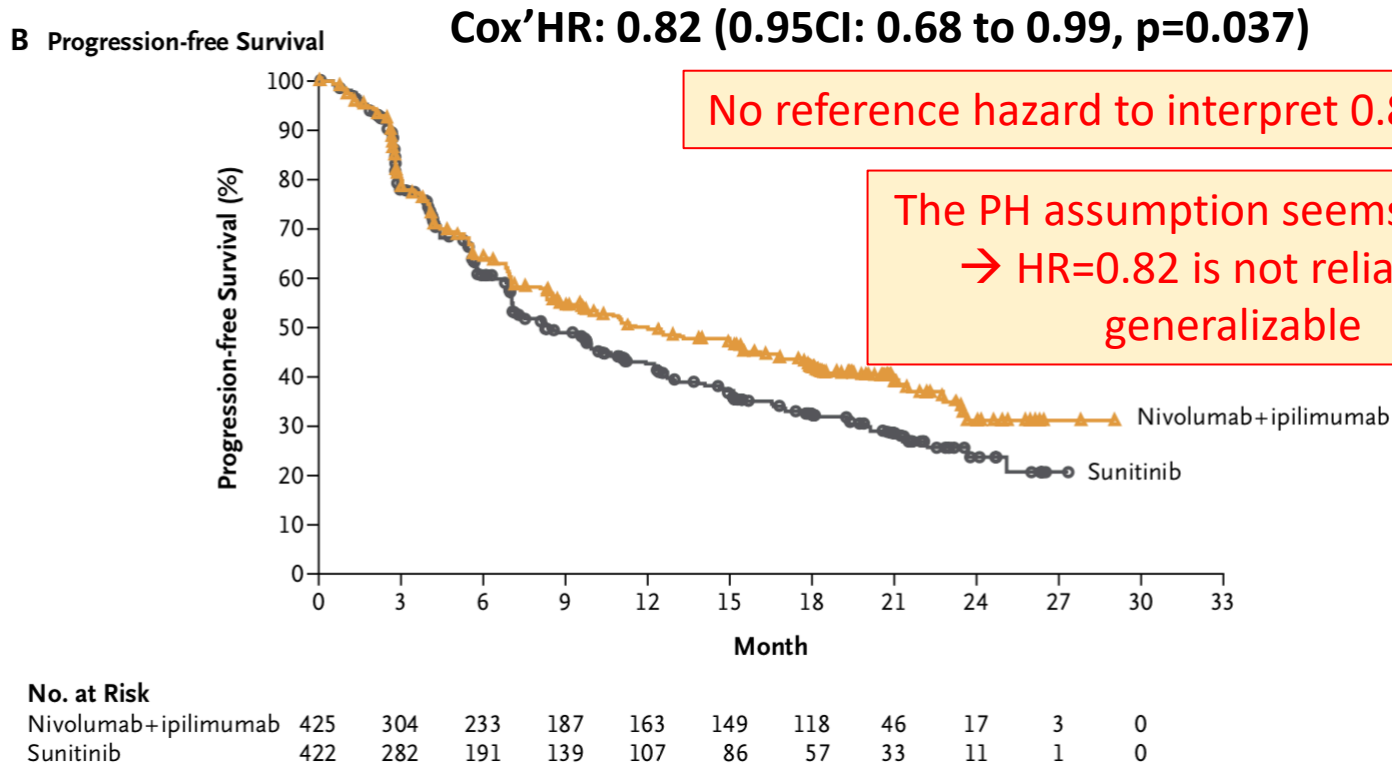
Authors often report results from analysis of survival or time-to-event data using hazard ratios estimated from proportional hazards Cox models. **Hazard ratios are notoriously difficult to interpret clinically, may be sensitive to the length of follow-up, and rely on model assumptions, such as proportional hazards. In addition, presenting estimates of effect in both absolute and relative terms increases the likelihood that results will be correctly interpreted.** For all of these reasons, we recommend that authors present cumulative incidence curves (inverted Kaplan-Meier plots) along with tabular summaries of absolute differences in cumulative incidence, with 95% confidence bounds, at meaningful times, when reporting results from survival analyses. When such an analysis requires covariate adjustment, authors can estimate and present covariate-standardized (weighted) cumulative incidence curves with differences in adjusted cumulative incidence at meaningful times.

HR cannot address a practically important recommendation

	Overall Survival (Study 1)	Overall Survival (Study 2)
Hazard Ratio	0.73	0.73
Hazard Difference	NA (small?)	NA (large?)
Hazard in Treatment group	NA	NA
Hazard in Control group	NA	NA

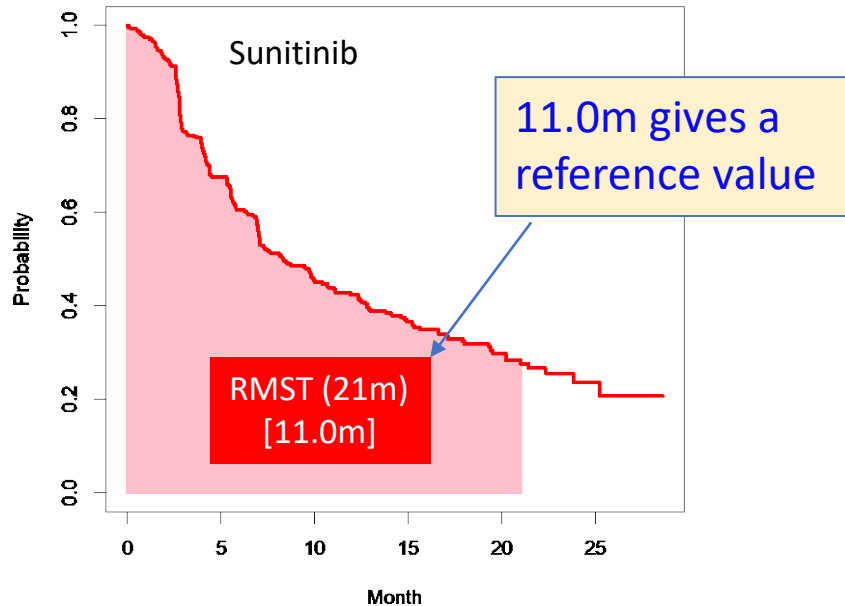
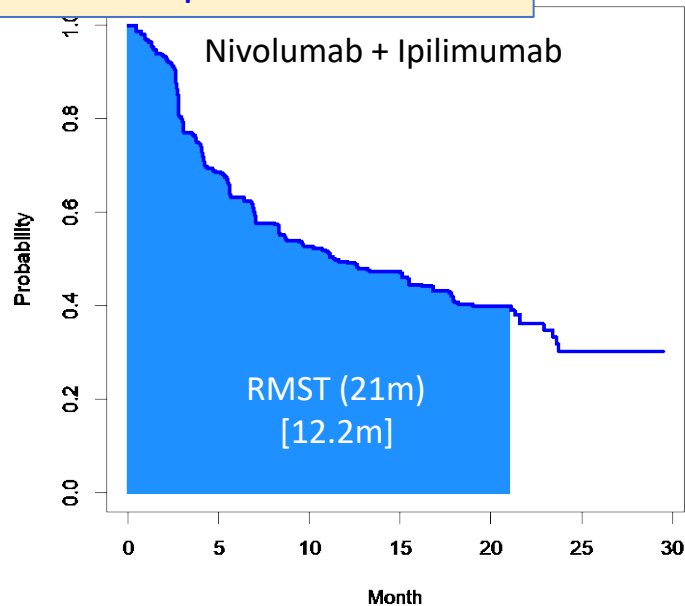
*Does **HR = 0.73** indicate the new treatment gives a clinically meaningful large effect?*

Recall: CheckMate 214: HR-approach



Recall: CheckMate 214: RMST approach

No model assumptions → Robust



Nivolumab +Ipilimumab vs. Sunitinib	Estimate	0.95 CI	p-value
Difference in RMST	1.2m	0.5m to 2.4m	0.041
Ratio of RMST	1.1	1.0 to 1.2	0.040

3. Applications of RMST approaches in prevention research

Example #1

BRIEF REPORTS

Journal of the American Geriatrics Society, 66(10), 1987–1991.

Pravastatin for Primary Prevention in Older Adults: Restricted Mean Survival Time Analysis

Ariela R. Orkaby, MD, MPH,^{*†} Michael W. Rich, MD,[‡] Ryan Sun, PhD,[§] Eliah Lux, BA,[¶]
Lee-Jen Wei, PhD,^{§,⊥} and Dae Hyun Kim, MD, MPH, ScD^{¶||,⊥} 

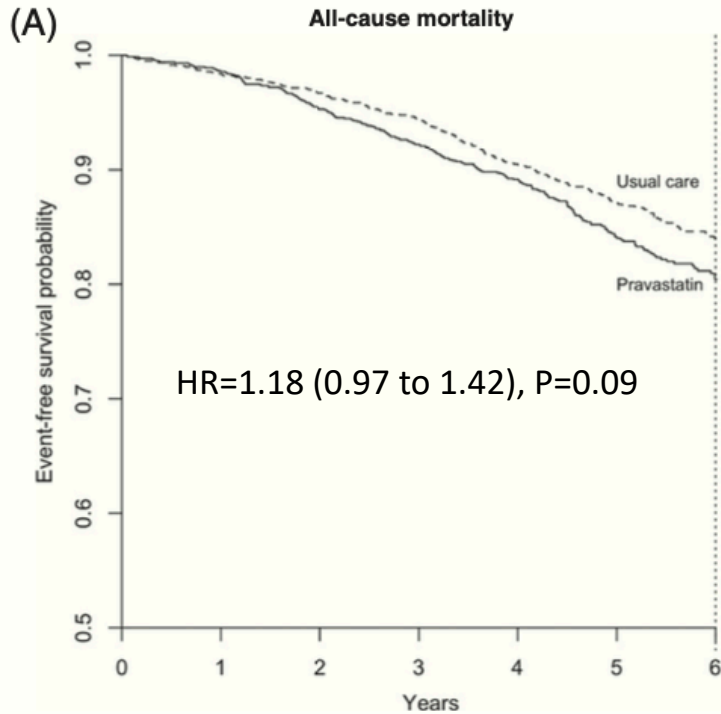
DESIGN: Secondary analysis of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial- Lipid-Lowering Trial (ALLHAT-LLT).

SETTING: Ambulatory setting.

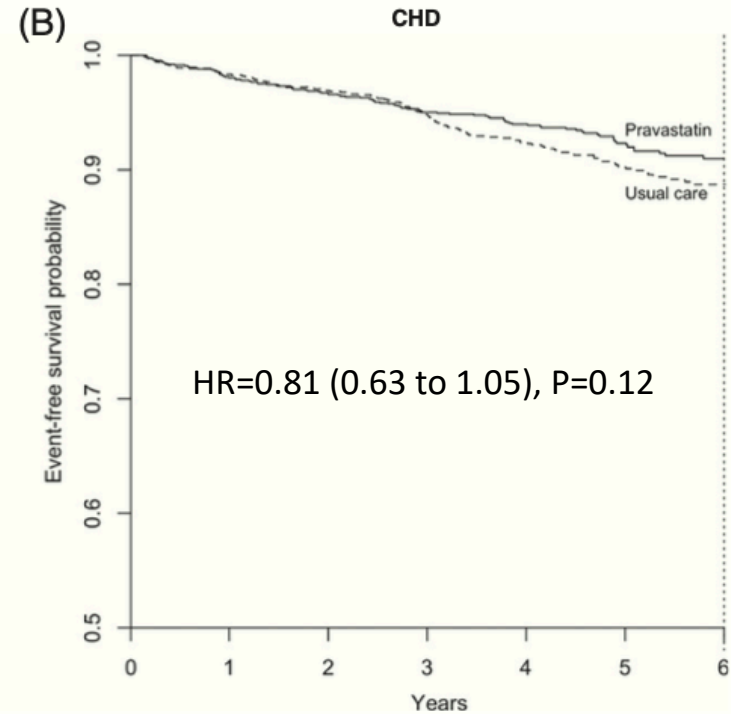
PARTICIPANTS: Individuals aged 65 and older (mean aged 71, 49% female) free of cardiovascular disease (N=2,867).

INTERVENTION: Pravastatin 40 mg/d (n=1,467) versus usual care (n=1,400).

MEASUREMENTS: All-cause mortality and coronary heart disease (CHD)-free survival over the 6-year trial period.



6-Year RMST Pravastatin Group (95% CI), days 2008.1 (1983.3, 2030.7)
6-Year RMST Usual Care Group (95% CI), days 2041.7 (2019.4, 2063.6)
Difference (Pravastatin - Usual Care) (95% CI), days -33.7 (-67.0, -0.5)
P=0.047



6-Year RMST Pravastatin Group (95% CI), days 2088.1 (2068.0, 2108.5)
6-Year RMST Usual Care Group (95% CI), days 2069.4 (2047.9, 2091.0)
Difference (Pravastatin - Usual Care) (95% CI), days 18.7 (-10.4, 47.8)
P=0.21

Message from Example #1

- RMST provides an intuitive, explicit way to express the effect of pravastatin on CHD-free and overall survival for primary prevention in older adults.
- RMST allows a more personalized interpretation of the benefits and risks of treatment than HRs.

CHARM-Overall Study

Articles

🕒 @ Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme

Marc A Pfeffer, Karl Swedberg, Christopher B Granger, Peter Held, John J V McMurray, Eric L Michelson, Bertil Olofsson, Jan Östergren, Salim Yusuf, for the CHARM Investigators and Committees*

Summary

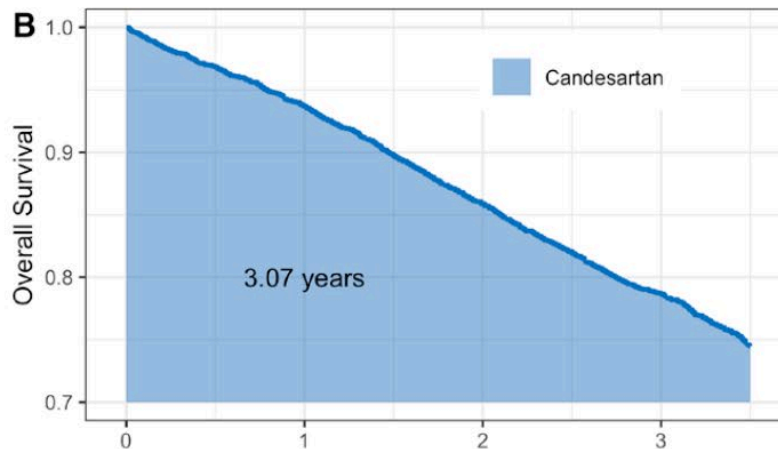
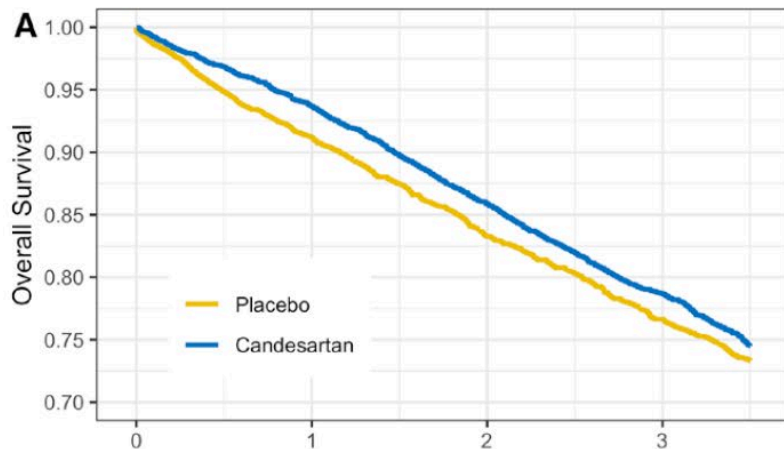
Background Patients with chronic heart failure (CHF) are at high risk of cardiovascular death and recurrent hospital admissions. We aimed to find out whether the use of an angiotensin-receptor blocker could reduce mortality and morbidity.

Methods In parallel, randomised, double-blind, controlled, clinical trials we compared candesartan with placebo in three distinct populations. We studied patients with left-ventricular ejection fraction (LVEF) 40% or less who were not receiving angiotensin-converting-enzyme inhibitors because of previous intolerance or who were currently receiving angiotensin-converting-enzyme inhibitors, and patients with LVEF higher than 40%. Overall, 7601 patients (7599 with data) were

Introduction

In patients with chronic heart failure (CHF) and reduced left-ventricular ejection fraction (LVEF), results of clinical randomised trials have shown the life-saving and symptomatic benefits of angiotensin-converting-enzyme inhibitors,¹⁻³ β blockers,⁴⁻⁷ and, in more selected patients, spironolactone.⁸ These findings have led to widespread use of these treatments in appropriate populations.⁹ The results have been translated into benefits in clinical practice, since in epidemiological studies and large registries substantial temporally related reductions have been seen in the age-adjusted mortality of patients with heart failure.¹⁰⁻¹² Despite these major successes, the prevalence of heart failure continues to increase, mainly as a consequence of ageing

All cause of death



HR: 0.91 (0.83 to 1.00; $p=0.055$)

The PH assumption was not met (Goodness-of-fit test: $p<0.001$)

RMST (3.5y) : **3.07 years** (Candesartan) vs. **3.00 years** (Placebo)

The difference of 0.07 years (95% CI, 0.03–0.11; **$P=0.0016$**) was highly statistically significant in favor of candesartan.

0.07 years is about 3.6 weeks.

Message from Example #2

- RMST can be more statistically efficient than HR when PH is not met
- After passing the statistical significance hurdle, the clinical utility of candesartan can be evaluated using individual RMSTs (3.07 and 3.00 years). For the present case, it is debatable whether the 0.07-year (3.6-week) survival gain is clinically significant

4. Regression Analysis for RMST

Importance of regression analysis in prevention research

- Adjusting for confounding factors when comparing interventions
- Investigating predictive factors for prognosis
- Investigating predictive factors for intervention
- Building risk prediction models to predict patient outcomes

How can we do with RMST?

Regression analysis for RMST

Model:

$$g\{E(\min(T, \tau) | Z, X)\} = \alpha + \beta Z + \boldsymbol{\gamma}' \mathbf{X}$$

where α is the intercept, Z is the indicator variable for the intervention (1: intervention, 0: control) and X is a covariate vector to be adjusted.

Link function: $g(x)$	Interpretation
$g(x) = x$	β : Difference in RMST
$g(x) = \log(x)$	e^β : Ratio of RMST
$g(x) = \log(\tau - x)$	e^β : Ratio of RMTL

Inference of regression parameters

- $Y_i = T_i \wedge C_i = \min(T_i, C_i)$ --- observed time (either event time or censoring time)
- $\delta_i = I(T_i \leq C_i)$ --- the event indicator (1: event, 0: censor)
- **Estimating equation**

$$Q = \sum_{i=1}^n \frac{I(Y_i \geq \tau) + I(Y_i < \tau)\delta_i}{\hat{K}(Y_i \wedge \tau)} \begin{pmatrix} 1 \\ Z_i \\ \mathbf{X}_i \end{pmatrix} [T_i \wedge \tau - g^{-1}(\alpha + \beta Z_i + \boldsymbol{\gamma}' \mathbf{X}_i)] = 0$$

- Inverse probability of censoring weighting method can be used.
- $\hat{K}(t)$ is the KM estimator of the survival function of the censoring distribution
- Note, here we assume C is independent of $(T, Z, \mathbf{X})$
- Solve $Q = 0$. Let $\hat{\alpha}$, $\hat{\beta}$, and $\hat{\boldsymbol{\gamma}}$ be the estimator for α, β , and $\boldsymbol{\gamma}$, respectively.
- $\hat{\alpha}$, $\hat{\beta}$, and $\hat{\boldsymbol{\gamma}}$ are consistent and asymptotically normal

See Tian et al. (2014, Biostatistics) for the details of the asymptotic properties of $\hat{\alpha}$, $\hat{\beta}$, and $\hat{\boldsymbol{\gamma}}$.

5. Practical implementation of RMST analysis using software packages

Implementation of RMST analysis

R

- survRM2
 - From the CRAN
 - From the github repo (newest version)
<https://github.com/uno1lab/survRM2>

Stata

- strmst2 command

SAS

- LIFETEST procedure (RMST option)
- RMSTREG procedure

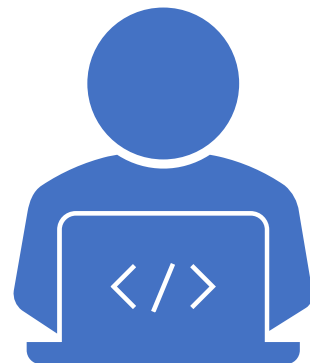


- R package “survRM2”
- Function “rmst2” is the main function
- Example R code:

```
#-- install package
devtools::install_github("uno1lab/survRM2")

D=rmst2.sample.data()
time=D$time
status=D$status
arm=D$arm
covs=D[,c(4,6,7)]

#--- 2 sample comparison ----
a=rmst2(time, status, arm, tau=10)
```



```
> print(a)
```

The truncation time: tau = 10 was specified.

Restricted Mean Survival Time (RMST) by arm

	Est.	se	lower .95	upper .95
RMST (arm=1)	7.146	0.283	6.592	7.701
RMST (arm=0)	7.283	0.295	6.704	7.863

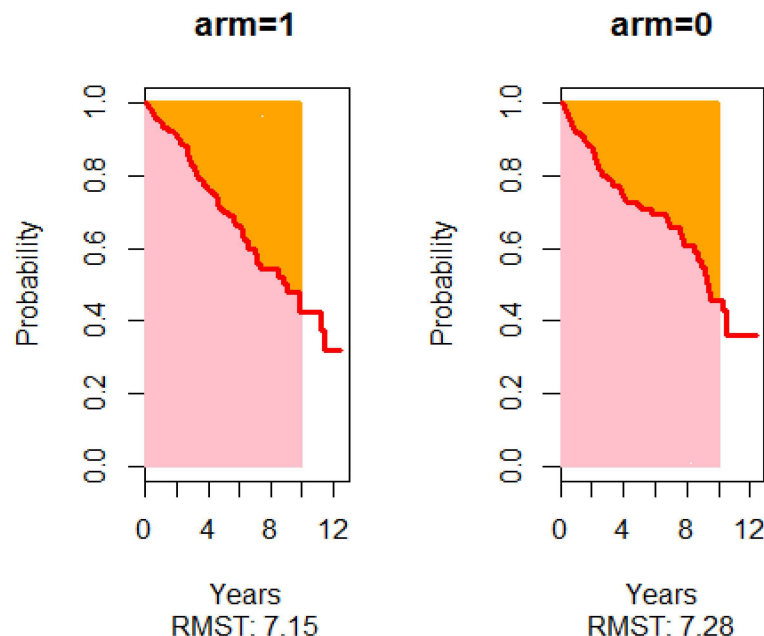
Restricted Mean Time Lost (RMTL) by arm

	Est.	se	lower .95	upper .95
RMTL (arm=1)	2.854	0.283	2.299	3.408
RMTL (arm=0)	2.717	0.295	2.137	3.296

Between-group contrast

	Est.	lower .95	upper .95	p
RMST (arm=1)-(arm=0)	-0.137	-0.939	0.665	0.738
RMST (arm=1)/(arm=0)	0.981	0.878	1.096	0.738
RMTL (arm=1)/(arm=0)	1.050	0.787	1.402	0.738

```
> plot(a, xlab="Years", ylab="Probability", density=60)
```



Regression analysis for RMST

#--- with covariates ----

rmst2(time, status, arm, tau=10, covariates=x)

Summary of between-group contrast (adjusted for the covariates)

	Estimate	[95% Conf. Interval]	P> z
RMST (arm 1 - arm 0)	-0.210	-0.883 0.463	0.540
RMST (arm 1 / arm 0)	0.968	0.877 1.068	0.514
RMTL (arm 1 / arm 0)	1.035	0.806 1.329	0.786

Model summary (difference of RMST)

	Coef.	Std. Err.	z	P> z	[95% Conf. Interval]
intercept	2.743	2.134	1.29	0.199	-1.440 6.627
treatment	-0.210	0.343	-0.61	0.540	-0.883 0.463
age	-0.069	0.018	-3.90	0.000	-0.103 -0.034
bili	-0.325	0.039	-8.39	0.000	-0.401 -0.249
albumin	2.550	0.472	5.40	0.000	1.624 3.475

Model summary (ratio of RMST)

	Coef.	Std. Err.	z	P> z	exp(Coef.)	[95% Conf. Interval]
intercept	1.369	0.356	3.84	0.000	3.930	1.955 7.899
treatment	-0.033	0.050	-0.65	0.514	0.968	0.877 1.068
age	-0.009	0.003	-3.41	0.001	0.991	0.985 0.996
bili	-0.087	0.013	-6.52	0.000	0.917	0.893 0.941
albumin	0.360	0.080	4.49	0.000	1.434	1.225 1.678

Model summary (ratio of time-lost)

	Coef.	Std. Err.	z	P> z	exp(Coef.)	[95% Conf. Interval]
intercept	1.992	0.695	2.86	0.004	7.332	1.876 28.655
treatment	0.035	0.127	0.27	0.786	1.035	0.806 1.329
age	0.025	0.007	3.81	0.000	1.026	1.012 1.039
bili	0.063	0.008	8.33	0.000	1.065	1.049 1.080
albumin	-0.750	0.149	-5.03	0.000	0.472	0.353 0.633



* install the strms2 command

```
ssc install strms2
```

```
net get strms2
```

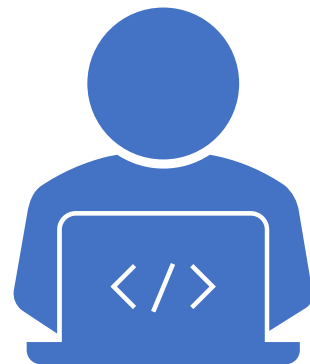
* load a sample datafile

```
use pbc, clear
```

```
stset time, f(status)
```

* Run (without covariates)

```
strms2 treatment, tau(10)
```



The truncation time: $\tau = 10$ was specified.

Restricted Mean Survival Time (RMST) by arm

Group	Estimate	Std. Err.	[95% Conf. Interval]
arm 1	7.146	0.284	6.589 7.704
arm 0	7.283	0.297	6.700 7.866

Restricted Mean Time Lost (RMTL) by arm

Group	Estimate	Std. Err.	[95% Conf. Interval]
arm 1	2.854	0.284	2.296 3.411
arm 0	2.717	0.297	2.134 3.300

Between-group contrast

Contrast	Estimate	[95% Conf. Interval]	P> z
RMST (arm 1 - arm 0)	-0.137	-0.943 0.669	0.739
RMST (arm 1 / arm 0)	0.981	0.877 1.097	0.739
RMTL (arm 1 / arm 0)	1.050	0.786 1.404	0.740

Regression analysis

* Run (with covariates)

strmst2 treatment, tau(10) covariates(age bili albumin)

Summary of between-group contrast (adjusted for the covariates)

	Estimate	[95% Conf. Interval]	P> z
RMST (arm 1 - arm 0)	-0.210	-0.883 0.463	0.540
RMST (arm 1 / arm 0)	0.968	0.877 1.068	0.514
RMTL (arm 1 / arm 0)	1.035	0.806 1.329	0.786

Model summary (difference of RMST)

	Coef.	Std. Err.	z	P> z	[95% Conf. Interval]
intercept	2.743	2.134	1.29	0.199	-1.440 6.627
treatment	-0.210	0.343	-0.61	0.540	-0.883 0.463
age	-0.069	0.018	-3.90	0.000	-0.103 -0.034
bili	-0.325	0.039	-8.39	0.000	-0.401 -0.249
albumin	2.550	0.472	5.40	0.000	1.624 3.475

Model summary (ratio of RMST)

	Coef.	Std. Err.	z	P> z	exp(Coef.)	[95% Conf. Interval]
intercept	1.369	0.356	3.84	0.000	3.930	1.955 7.899
treatment	-0.033	0.050	-0.65	0.514	0.968	0.877 1.068
age	-0.009	0.003	-3.41	0.001	0.991	0.985 0.996
bili	-0.087	0.013	-6.52	0.000	0.917	0.893 0.941
albumin	0.360	0.080	4.49	0.000	1.434	1.225 1.678

Model summary (ratio of time-lost)

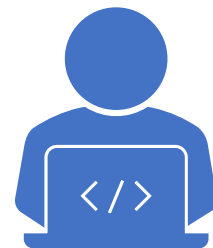
	Coef.	Std. Err.	z	P> z	exp(Coef.)	[95% Conf. Interval]
intercept	1.992	0.695	2.86	0.004	7.332	1.876 28.655
treatment	0.035	0.127	0.27	0.786	1.035	0.806 1.329
age	0.025	0.007	3.81	0.000	1.026	1.012 1.039
bili	0.063	0.008	8.33	0.000	1.065	1.049 1.080
albumin	-0.750	0.149	-5.03	0.000	0.472	0.353 0.633



Example SAS code:

```
% The LIFETEST procedure (RMST option) ;  
proc LIFETEST data=pbcr mst(tau=10);  
  strata arm;  
  time time*status(0);  
run;
```

```
% The RMSTREG procedure ;  
proc RMSTREG data=pbcr tau=10;  
  class arm;  
  model time*status(0) = arm / link=linear  
  method=ipcw(strata=arm) ;  
run;
```



Note: Without (strata=arm) option, the RMSTREG procedure will produce slightly different results from those R/Stata, because a common censoring distribution is assumed in RMSTREG without the strata option.

Regression

```
proc RMSTREG data=liver tau=10;  
  class arm;  
  model Time*Status(0) = arm age bilirubin albumin / link=linear method=ipcw ;  
run;
```

method=pv is also available in SAS/PROC RMSTREG

METHOD=*method*<(STRATA=*variable*)>

specifies the estimation method to fit the specified model. You can specify the *methods* shown in [Table 103.8](#).

Table 103.8: Estimation Methods of the RMSTREG Procedure

METHOD=	Estimation Method
PV	Pseudovalue regression (Andersen, Hansen, and Klein 2004)
IPCW	Inverse probability censoring weighting estimation (Tian, Zhao, and Wei 2014)

6. Summary

Summary

Key Takeaway:

- Providing the magnitude of intervention effects is crucial for decision making.
- The limitations of HR-based approaches in quantifying these effects are acknowledged.
- Consequently, RMST is gaining attention as an alternative to the conventional HR-based approach.
- RMST provides robust and clinically interpretable summaries of intervention effects, aiding in decision making.

Remarks:

- Today's talk covered only a limited number of RMST approaches, but there is a wide range of research in this area.

Other RMST Approaches: Topics Beyond This Talk

- Study design
- Empirical choice of a truncation time
- Power comparison between HR-based tests and RMST-based tests
- Stratified analysis
- Competing risks data
- Recurrent event time data
- Duration of response
- Quantifying long-term survival benefit
- Clustered data
- Non-randomized data
- Equivalence/non-inferiority trials

Please see the attached reference list for these topics we could not cover today

Acknowledgment

These presentation slides were developed in collaboration with Dr. Lu Tian (Stanford) and Dr. Lee-Jen Wei (Harvard).

I am grateful for the support from:

- The National Institute of General Medical Sciences of the National Institutes of Health (R01GM152449, PI: Hajime Uno)
- The McGraw/Patterson Research Fund

Contact Information

Hajime Uno, PhD

Department of Data Sciences

Department of Medical Oncology (Population Sciences)

Dana-Farber Cancer Institute/Harvard Medical School

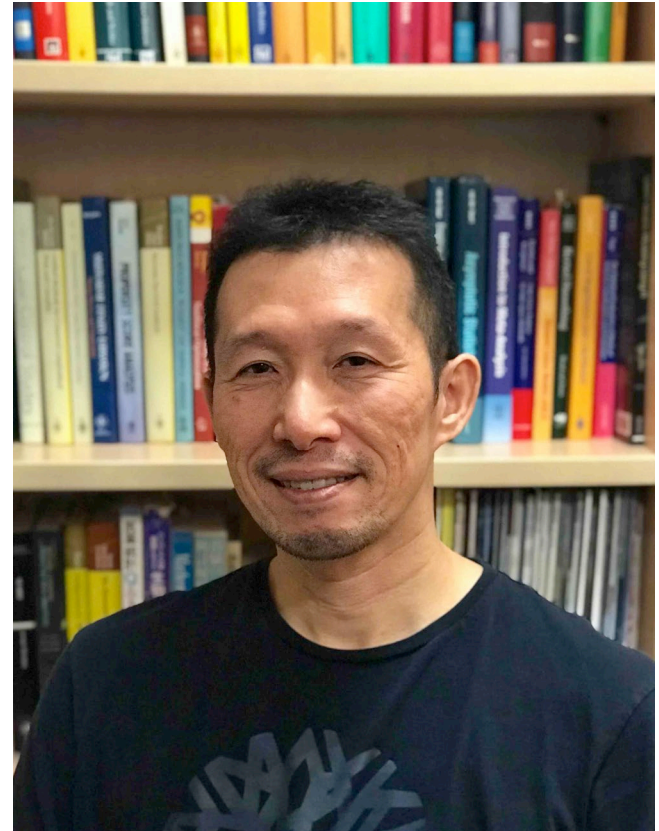
Address: 450 Brookline Avenue, Boston, MA 02215

Email: huno@ds.dfci.harvard.edu

URL: <https://ds.dfci.harvard.edu/~huno>

Twitter: [@unoichi3](https://twitter.com/unoichi3)

GitHub: [uno1lab](https://github.com/uno1lab), [unoichi](https://github.com/unoichi)



Thank you

Backup slides

Example: RMST was used for
the primary analysis

Rivaroxaban in Patients with Atrial Fibrillation and a Bioprosthetic Mitral Valve

ABSTRACT

BACKGROUND

The effects of rivaroxaban in patients with atrial fibrillation and a bioprosthetic mitral valve remain uncertain.

METHODS

In this randomized trial, we compared rivaroxaban (20 mg once daily) with dose-adjusted warfarin (target international normalized ratio, 2.0 to 3.0) in patients with atrial fibrillation and a bioprosthetic mitral valve. The primary outcome was a composite of death, major cardiovascular events (stroke, transient ischemic attack, systemic embolism, valve thrombosis, or hospitalization for heart failure), or major bleeding at 12 months.

RESULTS

A total of 1005 patients were enrolled at 49 sites in Brazil. A primary-outcome event occurred at a mean of 347.5 days in the rivaroxaban group and 340.1 days in the warfarin group (difference calculated as restricted mean survival time, 7.4 days; 95% confidence interval [CI], -1.4 to 16.3; $P < 0.001$ for noninferiority). Death from cardiovascular causes or thromboembolic events occurred in 17 patients (3.4%) in the rivaroxaban group and in 26 (5.1%) in the warfarin group (hazard ratio, 0.65; 95% CI, 0.35 to 1.20). The incidence of stroke was 0.6% in the rivaroxaban group and 2.4% in the warfarin group (hazard ratio, 0.25; 95% CI, 0.07 to 0.88). Major bleeding occurred in 7 patients (1.4%) in the rivaroxaban group and in 13 (2.6%) in the warfarin group (hazard ratio, 0.54; 95% CI, 0.21 to 1.35). The frequency of other serious adverse events was similar in the two groups.

CONCLUSIONS

In patients with atrial fibrillation and a bioprosthetic mitral valve, rivaroxaban was noninferior to warfarin with respect to the mean time until the primary outcome of death, major cardiovascular events, or major bleeding at 12 months. (Funded by PROADI-SUS and Bayer; RIVER ClinicalTrials.gov number, NCT02303795.)

RMST was used as the primary analysis

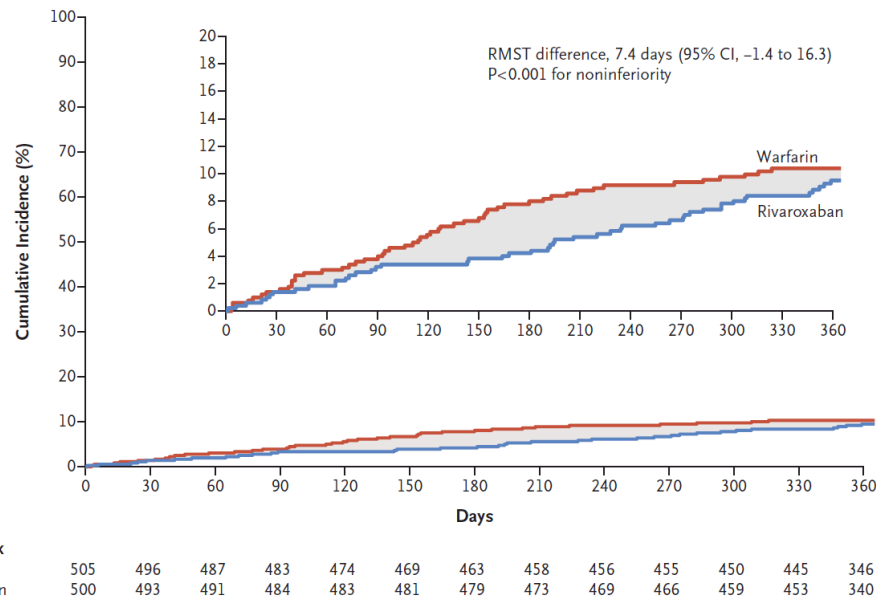


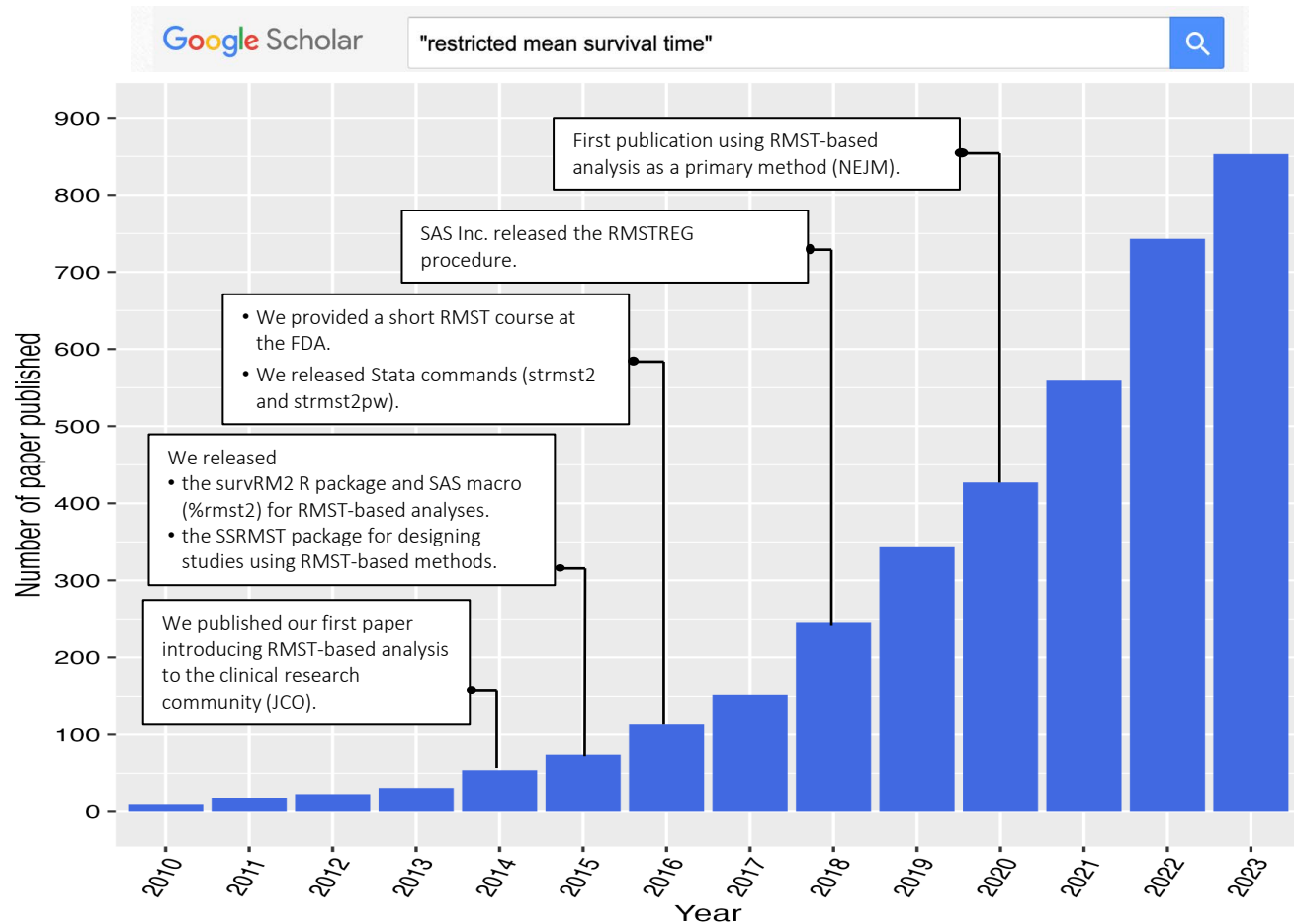
Figure 1. Kaplan–Meier Analysis of the Primary Outcome.

Shown is the primary outcome (death, major cardiovascular events, or major bleeding) in the rivaroxaban group and the warfarin group, as calculated according to the restricted mean survival time (RMST) method. The inset shows the same data on an expanded y axis.

Activities and Events

RMST was proposed
by Irwin (1947)

Karrison
(1997, Cont.Clin.Trial)



Study Design

Study Design for RCT

- Consider the meaningful follow-up time
- Consider the reference survival curve and RMST in the placebo group
- Consider the clinically meaningful and plausible treatment effect in terms of RMST
- Consider the enrollment pattern and censoring distribution
 - Accrual profile (accrual rate, accrual period, accrual pattern)
 - Additional follow-up time after the completion of the accrual

Sample Size Formula

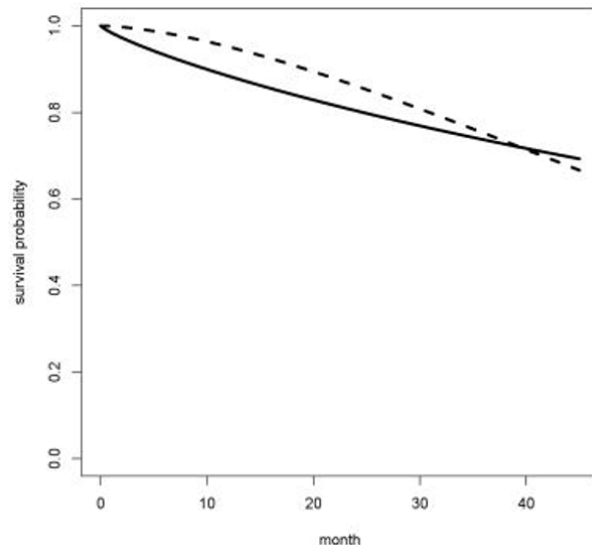
- Type one error α
- Power $1 - \beta$
- The sample size needed is

$$N = \frac{(z_{1-\alpha/2} + z_{1-\beta})^2 \int_0^t \left[\frac{\left\{ \int_v^t S_0(u) du \right\}^2 \lambda_0(v)}{p_0 \pi_0(v)} + \frac{\left\{ \int_v^t S_1(u) du \right\}^2 \lambda_1(v)}{p_1 \pi_1(v)} \right] dv}{\left[\int_0^t \{S_1(u) - S_0(u)\} du \right]^2}$$

where $\lambda_j(v)$ is the hazard function, $\pi_j(v)$ is the at risk proportion (depending on the censoring distribution) and p_j is the proportion in arm j.

Example

- We assume that
 - The underlying survival distributions in two arms follow the two Weibull's (crossing hazards)
 - The study lasts for 40 months with a 20-month enrollment period.
 - The time of loss of follow up follow an exponential distribution with an annual drop-off rate of 5% .
- The required sample size for 80% power and $\alpha = 0.05$ was
 - 1407 per arm for [the HR-based test](#)
 - 608 per arm for the RMST-based test
- Check: The empirical power based on 5000 simulations was
 - 79.7% for HR-based test
 - 79.6% for RMST-based test





SSRMST package (from CRAN)

- Simulation based
- Example R code:

```
# Superiority test
```

```
ssrmst(ac_rate=15, ac_period=35, tot_time=510,  
tau=500, scale0=8500, scale1=8500)
```

```
# Non-inferiority test
```

```
ssrmst(ac_rate=15, ac_period=35, tot_time=510,  
tau=500, scale0=8500, scale1=8500, margin=18)
```

Output

Non-inferiority test

	Total	arm0	arm1
Sample size	524	262	262
Expected number of events	31	16	15
Power (separate)			
	0.95		
Power (pooled)			
	0.95		

SSRMST (Arguments)

ac_rate	Accrual rate: the number of patients per unit time.
ac_period	Accrual period: the time point at last accrual.
ac_number	Accrual number: the total number of accrual patients.
tot_time	Total study time: the time point at last follow-up.
tau	Truncation time point to calculate RMSTs.
shape0, shape1	Shape parameters for the Weibull distribution in both the control (arm0) and the treatment (arm1).
scale0, scale1	Scale parameters for the Weibull distribution in both the control (arm0) and the treatment (arm1). Note that when the PH assumption is assumed, the value of the scale parameter in the treatment (arm1) needs to be larger than or equal to that in the control (arm0), because the difference of the RMSTs (arm1 minus arm0) is of interest.
margin	Non-inferiority margin: a clinically acceptable difference in RMST. A value of minus margin is used to evaluate the power. When default (margin = 0), a superiority test is selected.
allocation1	Proportion of patients allocated to the treatment (arm1). Default value is 0.5.
one_sided_alpha	Nominal type I error level as one-sided. When default (one_sided_alpha = 0.025), 0.95 confidence intervals of the difference in RMST are estimated to calculate the power.
seed	Random seed used for the sampling. Default is NULL.
ntest	Number of iterations. When default (ntest = 2000), 2,000 sets of realizations are generated for calculating confidence intervals of RMST differences.



RMSTDesign package (<https://anneae.github.io/RMSTdesign/>)

- Based on the analytic variance
- Only superiority or inferiority (no non-inferiority)
- Can calculate
 - N given power
 - power given N

- Example R code:

```
devtools::install_github("anneae/RMSTdesign")  
library(RMSTdesign)
```

```
con<-survdef(times = 3, surv = 0.5)  
trt<-survdef(times = 4, surv = 0.5)  
RMSTpow(con, trt, k1 = 1, k2 = 3, tau = 3, power = 0.8)  
RMSTpow(con, trt, k1 = 1, k2 = 3, tau = 3, n = 1024)
```

k1: accrual period (assume uniform accrual)

k2: length of additional follow-up time