Literature-based Meta-analysis of adverse events accounting for heterogeneous follow-up period in oncology clinical trials

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Background

Collecting and reporting information on occurrence of adverse events (AE) is a very important part of clinical trials to discuss usefulness of treatments.

Incidence proportion (number of AE occurrence/number of subjects) is routinely reported.

- Useful as an initial summary
- But, if follow-up periods are different between treatment groups, incidence proportion is hard to interpret.

Use of survival analysis techniques is of interest for AE analysis (SAVYY project)

- More relevant summary
- But, hardly applied at least all the AEs.

Background

A single study can give very limited information on AE. Then, meta-analysis (MA) is expected to be useful.

FDA guidance# summarizes issues in MA for AE

- Sparsity
- Heterogeneous follow-up durations

In oncology clinical trials, AE is designed to be followed until PFS (plus alpha) or OS. Then, the follow-up duration is inconsistent among treatment groups.

- Simple aggregation of incidence proportions would not be appealing.

#: FDA Guidance for Industry:
Meta-Analysis of Randomized Controlled Trials to Evaluate the Safety of Human Drugs or Biological Products.

Objective and outline

Objective:

To propose methods to summarize occurrence of AEs accounting for heterogeneous follow-up durations.

Outline:

1. Motivating example
2. New proposal
3. Application to a real dataset
4. Simulation study
5. Discussion

Motivating example

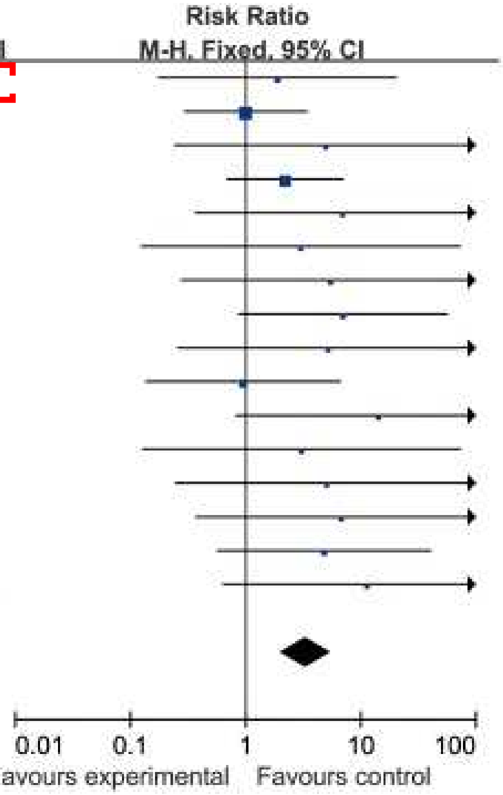
A meta-analysis of celebrovascular events for patients of various cancer-type treated by Bevacizmab

Forest plot of enrolled studies:

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Aghajanian, 2012	2	247	1	233	5.4%	1.89 [0.17, 20.67]
Allegra, 2009	5	1326	5	1321	26.1%	1.00 [0.29, 3.43]
Burger, 2011	2	608	0	601	2.6%	4.94 [0.24, 102.73]
Chinot, 2014	9	461	4	450	21.1%	2.20 [0.68, 7.08]
Giantonio, 2007	3	287	0	285	2.6%	6.95 [0.36, 133.97]
Herbst, 2011	1	313	0	313	2.6%	3.00 [0.12, 73.36]
Kabbinavar, 2003	2	32	0	35	2.5%	5.45 [0.27, 109.49]
Kelly, 2012	7	504	1	505	5.2%	7.01 [0.87, 56.80]
Kindler, 2007	2	53	0	55	2.6%	5.19 [0.25, 105.54]
Kindler, 2010	2	277	2	263	10.7%	0.95 [0.13, 6.69]
Miller, 2007	7	365	0	346	2.7%	14.22 [0.82, 248.06]
Okines, 2013	1	99	0	101	2.6%	3.06 [0.13, 74.23]
Perren, 2011	2	745	0	753	2.6%	5.05 [0.24, 105.09]
Price, 2012	4	315	0	236	3.0%	6.75 [0.37, 124.76]
Rini, 2010	5	362	1	347	5.3%	4.79 [0.56, 40.82]
Sandler, 2006	5	427	0	440	2.6%	11.33 [0.63, 204.35]
Total (95% CI)		**6421**		**6284**	**100.0%**	**3.28 [1.97, 5.48]**
Total events	59		14			

Heterogeneity: Chi² = 8.95, df = 15 (P = 0.88); I² = 0%

Test for overall effect: Z = 4.56 (P < 0.00001)



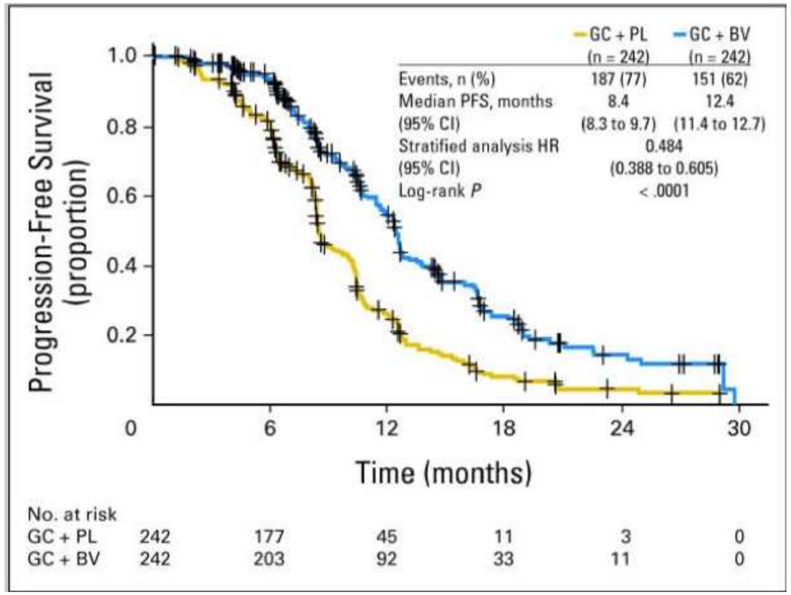
Zuo et al. (2014, Plos One)

The first study

Aghajanian et al. (2012, *J Clin Oncol*)
Doubly masked Phase 3 RCT for patients of uterine cancer
BV (n=247) against placebo (n=233)

Primary endpoint: PFS
Study end: PFS plus 1 month (until when AE is followed)

Primary analysis for efficacy: KM



Analysis of safety: Incidence proportion

BV： $\hat{p}_{AE}={}^{2}/_{247} \cong 0.008$
CT： $\hat{p}_{AE}={}^{1}/_{233} \cong 0.004$

KM for PFS suggests BV has longer follow-up duration.

Incidence proportion is hard to interpret.

Standard practice in oncology clinical trials

From ethical viewpoints, AE is designed to be followed until the primary endpoint (PFS, OS) is confirmed.

The result for the primary endpoint is usually summarized graphically with the Kaplan-Meier estimates.

In words, we may get information of the follow-up durations of AEs.

Idea: estimate cumulative distribution functions of time-to-AE using KM for PFS/OS.

Notation

Consider meta-analysis of AEs in RCTs of two treatments (k=1/0) in oncology

Assumptions on individual RCTs

Primary endpoint: PFS or OS
Follow-up of AE: until OS or PFS+α (say, 1 month)
For simplicity, PFS is the primary endpoint and the end of follow-up for all the studies (α=0).

Notation

For i=1,2,…, $n_k^{(s)}$

- $T_{k,i}^{(s)}$: time-to-PFS
- $C_{k,i}^{(s)}$: censoring for PFS
- $T_{k,i}^{(s)\ follow} = \min(T_{k,i}^{(s)}, C_{k,i}^{(s)})$: observed end of follow-up for AE
- $T_{k,i}^{(s)\ AE}$: time-to-AE

- $F_k^{(s)}(t) = P(T_{k,i}^{(s)} \leq t)$, $S_k^{(s)}(t)$ =1- $F_k^{(s)}(t)$
- $F_k^{(s)\ follow}(t) = P(T_{k,i}^{(s) follow} \leq t)$, $S_k^{(s) follow}(t)$ =1- $F_k^{(s)\ follow}(t)$

Distribution of AE is assumed common across studies;
- $F_k^{AE}(t) = P(T_{k,i}^{AE} \leq t)$, $S_k^{AE}(t)$ =1- $F_k^{AE}(t)$

Data

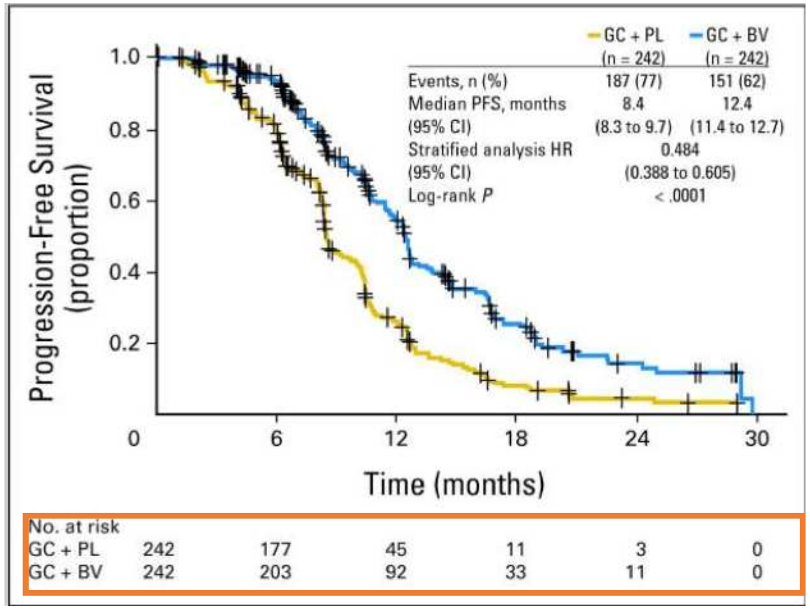
For s=1,2,…,S: the studies k=1/0: the treatment group,
The followings are supposed to be observed;

$n_k^{(s)}$:the number of subjects

$X_k^{(s)}$: the number of AE of interest

$\hat{S}_k^{(s)}(t)$:KM for PFS extracted by a graph-scan software such as Dizitizer

At-risk data attached to KM for PFS



at risk data

Key idea of our proposal

Incidence proportion:

$$
\begin{aligned}
p_k^{(s)} &= P\left(T_{k,i}^{(s)\,AE} \ \le\ T_{k,i}^{(s)\,follow}\right) \\
&= \int_0^{\infty} P\left(T_{k,i}^{(s)\,AE} \le t \,\middle|\, T_{k,i}^{(s)\,follow} = t\right) dF_k^{(s)follow}(t) \\
&= \int_0^{\infty} P\left(T_{k,i}^{(s)\,AE} \le t\right) dF_k^{(s)follow}(t) \qquad \text{If independent}
\end{aligned}
$$

- For $P\left(T_{k,i}^{(s)\,AE} \le t\right)$, some parametric survival model is supposed. This is free from the follow-up duration and thus can be compared between treatments.

Two settings are considered;

- Independent follow-up: $T_{k,i}^{(s)\,AE} \perp T_{k,i}^{(s)\,follow}$
- Dependent follow-up

Kawaguchi and Hattori (2026, RSM)

Proposed method: independent follow-up

With $T_{k,i}^{(s)\,AE} \perp T_{k,i}^{(s)\,follow}$

$$p_k^{(s)} = \int_0^\infty P\left(T_{k,i}^{(s)\,AE} \le t \middle| T_{k,i}^{(s)\,follow} = t\right) dF_k^{(s)follow}(t)$$

$$= \int_0^\infty P\left(T_{k,i}^{(s)\,AE} \le t\right) d\left\{1 - S_k^{(s)}(t)\ P\left(C_{k,i}^{(s)} \ge t\right)\right\}$$

Assume some parametric model

Kaplan-Meier for PFS

Estimate assuming exponential dist. using at-risk data

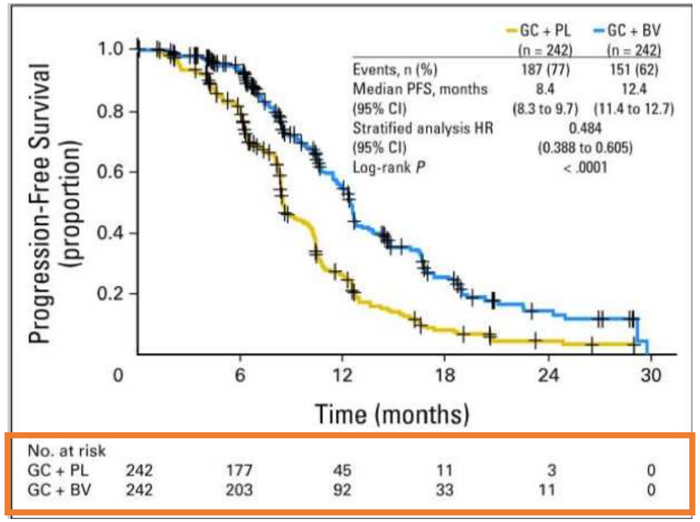
$$p_k^{(s)}(\theta_k) = \int_0^\infty P\left(T_{k,i}^{(s)\,AE} \le t; \theta_k\right) d\left\{1 - \hat{S}_k^{(s)}(t)\ \hat{P}\left(C_{k,i}^{(s)} \ge t\right)\right\}$$

Regarding $X_k^{(s)} \sim Binomial(n_k^{(s)}, p_k^{(s)}(\theta_k))$ approximately, estimate θ_k via maximum likelihood.

Proposed method: estimation of censoring dist.

Assume $T_{k,i}^{(s)} \perp C_{k,i}^{(s)}$.

Then, $E\left(min\left(T_{k,i}^{(s)}, C_{k,i}^{(s)}\right)\right) = S_k^{(s)}(t)\, P\left(C_{k,i}^{(s)} \geq t\right)$.



$Y_k^{(s)}(t)$

Assume a study-specific parametric model,

$P\left(C_{k,i}^{(s)} \geq t;\ \gamma_k^{(s)}\right)$

Estimation: min $\sum\left(\frac{Y_k^{(s)}(t)}{n_k^{(s)}} - \hat{S}_k^{(s)}(t)\, P\left(C_{k,i}^{(s)} \geq t; \gamma_k^{(s)}\right)\right)^2$

$Y_k^{(s)}(t)$:the number of at-risk subjects at time t.

The sum is taken over the points with $Y_k^{(s)}(t)$ reported.

$\hat{P}\left(C_{k,i}^{(s)} \geq t\right) = P\left(C_{k,i}^{(s)} \geq t; \hat{\gamma}_k^{(s)}\right)$

Proposed method: dependent follow-up

Dependence between $T_{k,i}^{(s)\,AE} \perp T_{k,i}^{(s)\,follow}$ is modeled with a parametric copula C_{ψ_k}

$$P\left(T_{k,i}^{(s)\,AE} \le t, T_{k,i}^{(s)\,follow} \le t\right)$$
$$=C_{\psi_k}\left(P\left(T_{k,i}^{(s)\,AE} \le t;\ \theta_k\right), P\left(T_{k,i}^{(s)\,follow} \le t\right)\right)$$
$$=C_{\psi_k}\left(P\left(T_{k,i}^{(s)\,AE} \le t; \theta_k\right), 1 - \ S_k^{(s)}(t)\ \ P\left(C_{k,i}^{(s)} \ge t\right)\right)$$
$$\cong C_{\psi_k}\left(P\left(T_{k,i}^{(s)\,AE} \le t; \theta_k\right), 1 - \hat{S}_k^{(s)}\ (t)\ \hat{P}\left(C_{k,i}^{(s)} \ge t\right)\right)$$

Proposed method: dependent follow-up

$$p_k^{(s)} = \int_0^\infty P\left(T_{k,i}^{(s)\,AE} \le t \middle| T_{k,i}^{(s)\,follow} = t\right) dF_k^{(s)follow}(t)$$

$$= \int_0^\infty \frac{P(T_{k,i}^{(s)\,AE} \le t \quad , T_{k,i}^{(s)\,follow} = t)}{P(T_{k,i}^{(s)\,follow} = t\ )} dF_k^{(s)follow}(t)$$

Assume some parametric survival model

$$= \int_0^\infty \frac{\partial}{\partial u} C_{\psi_k}\left(P\left(T_{k,i}^{(s)\,AE} \le t;\theta_k\right), u\right)\Big|_{u=F_k^{(s)follow}(t)} dF_k^{(s)follow}(t)$$

Assume some parametric copula

$$p_k^{(s)}\ (\theta_k, \psi_k) = \int_0^\infty \frac{\partial}{\partial u} C_{\psi_k}\left(P\left(T_{k,i}^{(s)\,AE} \le t;\theta_k\right), u\right)\Big|_{u=1-\hat{S}_k^{(s)}\ (t)\ \hat{P}\left(C_{k,i}^{(s)} \ge t\right)} d\left\{1 - \hat{S}_k^{(s)}\ (t)\ \hat{P}\left(C_{k,i}^{(s)} \ge t\right)\right\}$$

Regarding $X_k^{(s)} \sim Binomial(n_k^{(s)}, p_k^{(s)}\ (\theta_k, \psi_k))$ approximately, estimate (θ_k, ψ_k) via maximum likelihood.

Application to motivating data

Zuo et al. (2014): A meta-analysis of celebrovascular events for patients of various cancer-type treated by Bevacizmab

No.	Study ID	n	Primary endpoint	Follow-up	KM	At-risk
1	Aghajanian, 2012	480	PFS	PFS+1 (Mo)	○	○
2	Allegra, 2009	2,647	AE incidence	NA	×	×
3	Burger 2011	1,209	PFS	PFS+1 (Mo)	○	○
4	Chinot 2014	921	OS, PFS	PFS+3 (Mo)	○	○
5	Giantonio, 2007	572	OS	OS	○	×
6	Herbst, 2011	626	OS	OS	○	○
7	Kabbinavar, 2003	102	PFS	NA	×	×
8	Kelly, 2012	1,009	OS	PFS+1 (Mo)	○	○
9	Kim, 2012	212	PFS	PFS+1 (Mo)	○	○
10	Kindler, 2007	108	PFS	NA	×	×
11	Kindler, 2010	540	OS	OS	○	×
12	Miller, 2007	711	PFS	OS	○	○
13	Okines, 2013	200	GI perforation rates	NA	×	×
14	Perren, 2011	1,528	OS, PFS	PFS+1.5 (Mo)	○	○
15	Price, 2012	471	OS, PFS	NA	×	×
16	Rini, 2010	709	OS	OS	○	○
17	Sandler, 2006	867	OS	OS	○	×

11 studies had KM. Study 3 and 5 had two Bevacizmab groups.

Bevacizmab group: S=13, Control group: S=11

Application to motivating data

study	Primary endpoint	Kaplan-Meier	end of follow-up time	at risk data	n	Difference of MST (BV-CT)
1	PFS	○	PFS+1month	○	480	4
3	PFS	○	PFS+1month	○	1209	3.8
4	OS,PFS	○	PFS+3month	○	911	4.4
5	OS	○	OS	×	572	2.1
6	OS	○	OS	○	626	0.1
8	OS	○	PFS+1month	○	1009	1.1
9	PFS	○	PFS+1month	○	212	3.7
12	PFS	○	PFS+1month	○	711	5.9
14	OS,PFS	○	PFS+1.5month	○	1528	1.7
16	OS	○	OS	○	709	0.9
17	OS	○	OS	×	867	2

	n	AE
BV	5580	44
CT	4605	10

On average, BV group had 2.7 month longer follow-up duration.

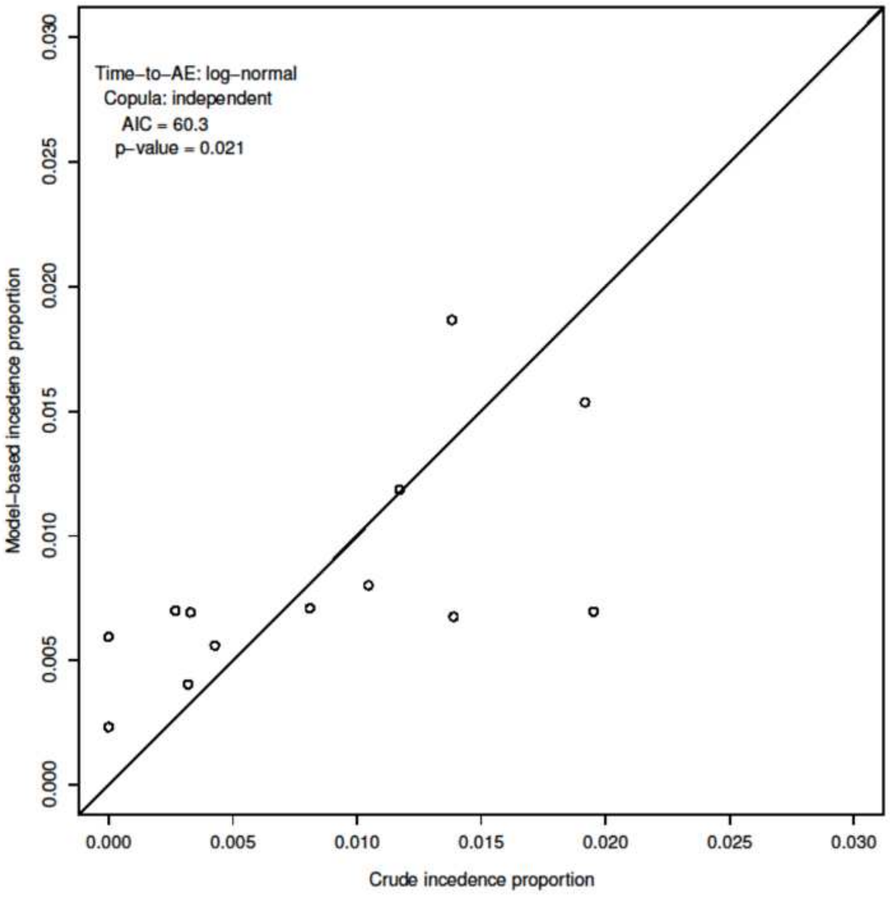
Application to motivating data

AIC for model-comparison

		Bevacizumab group			Control group		
Follow-up	Copula	Exponential	Weibull	Log-normal	Exponential	Weibull	Log-normal
Independent	Independent	62.3	60.7	60.7	34.2	NA	NA
Dependent	Clayton	63.4	63.4	63.5	36.0	NA	35.6
	Frank	64.0	62.4	62.1	35.1	NA	NA
	Gumbel	64.4	62.1	61.6	33.9	35.9	45.7

Application to motivating data: under independent follow-up

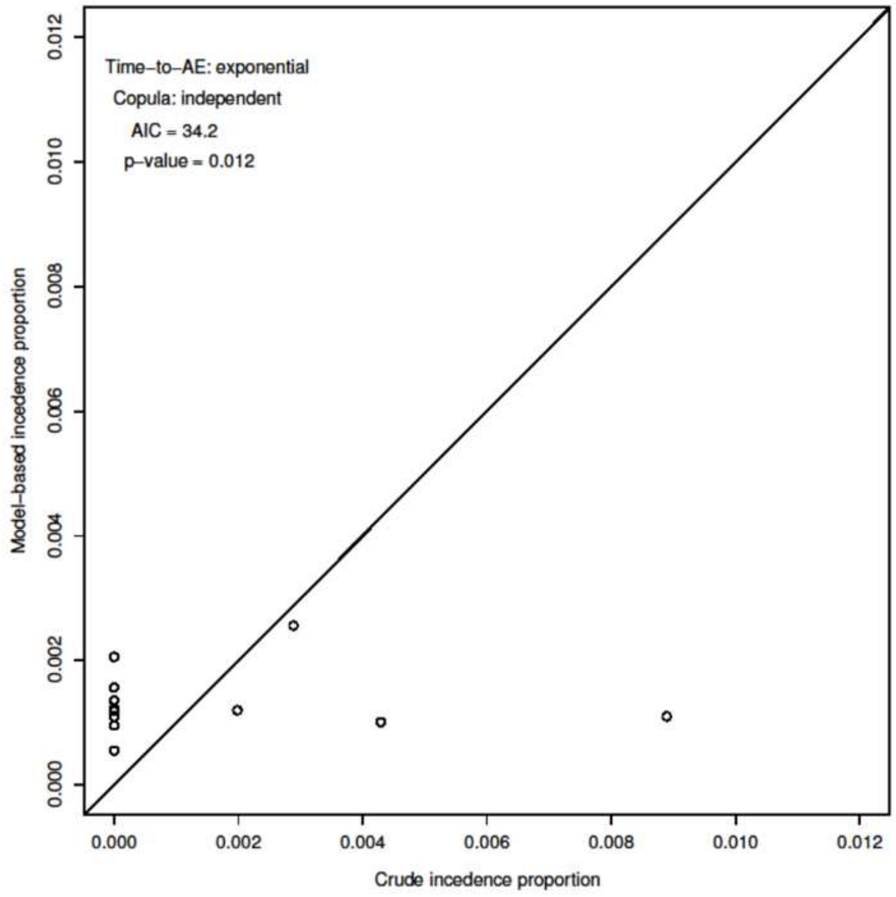
BV group



Model-based incidence proportion

Crude incidence proportion

CT group

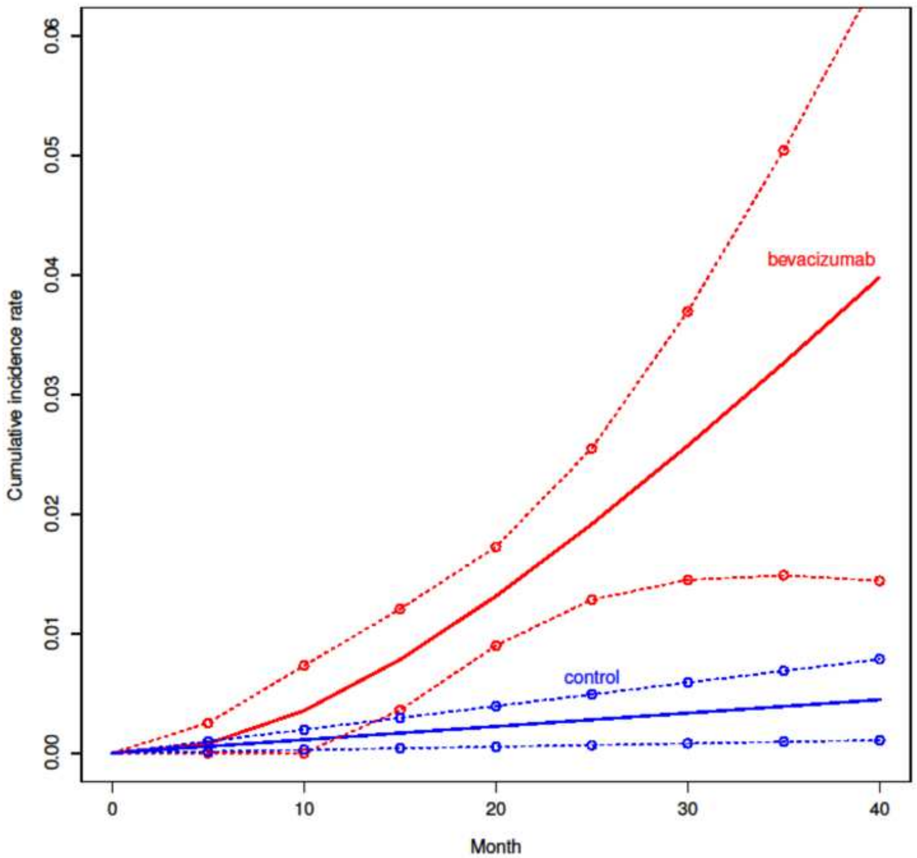


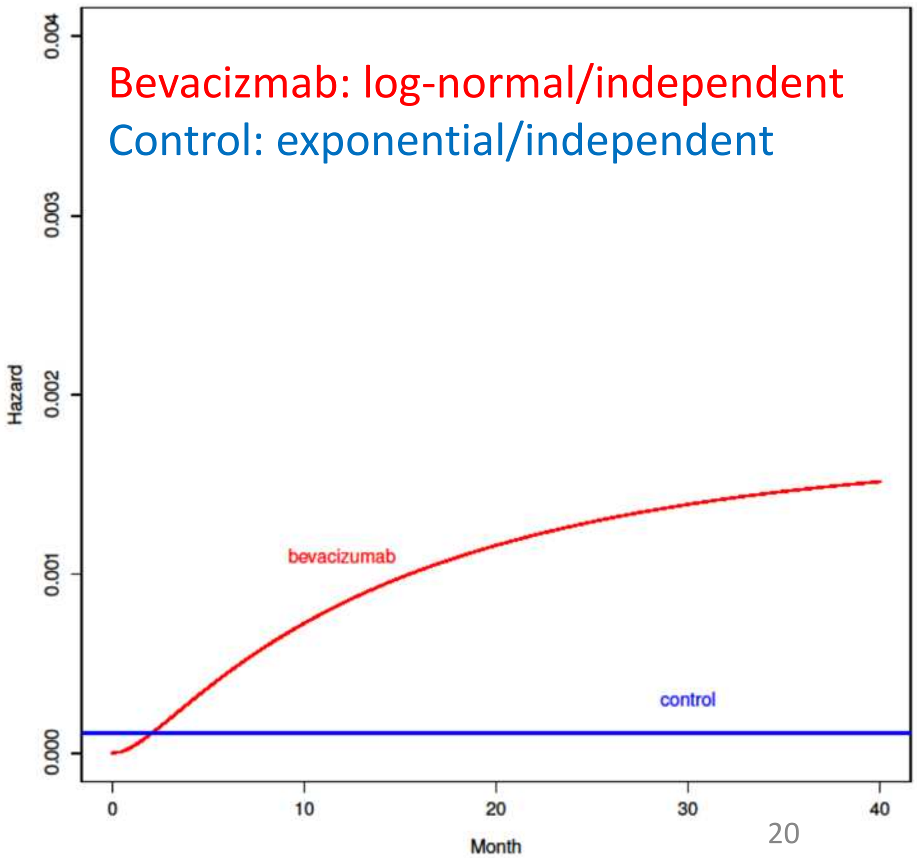
Crude incidence proportion

Application to motivating data: under independent follow-up

$P\left(T_{k,i}^{(s)\ AE} \leq t : \hat{\theta}_k\right)$
with the best model w.r.t AIC

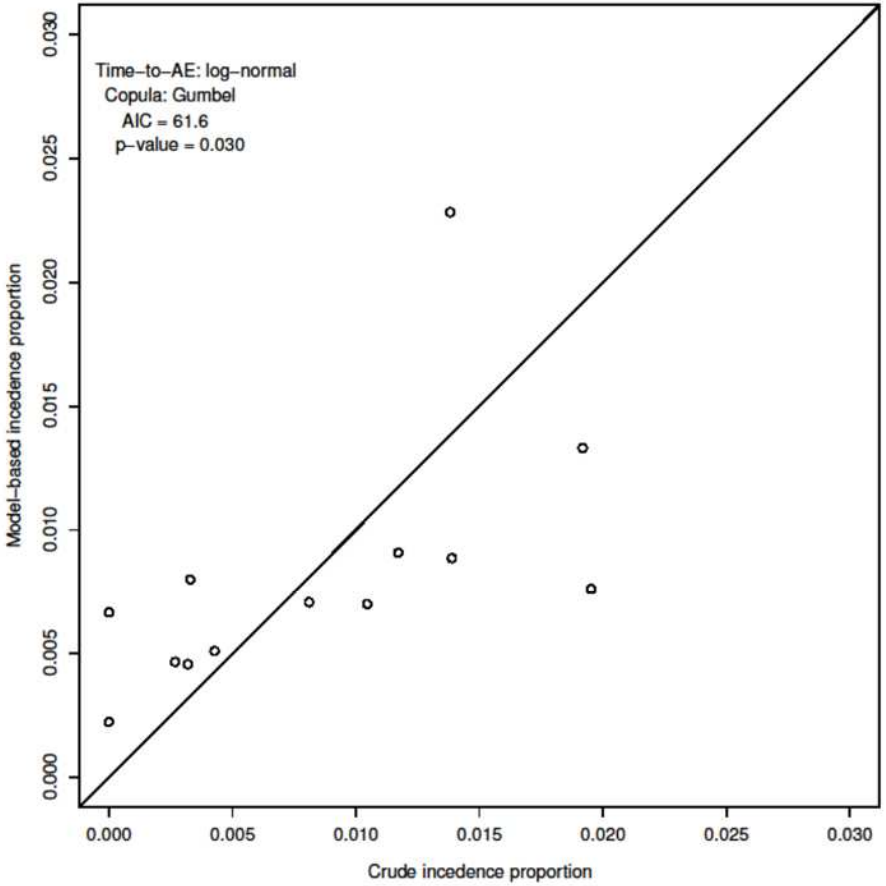
Hazard function



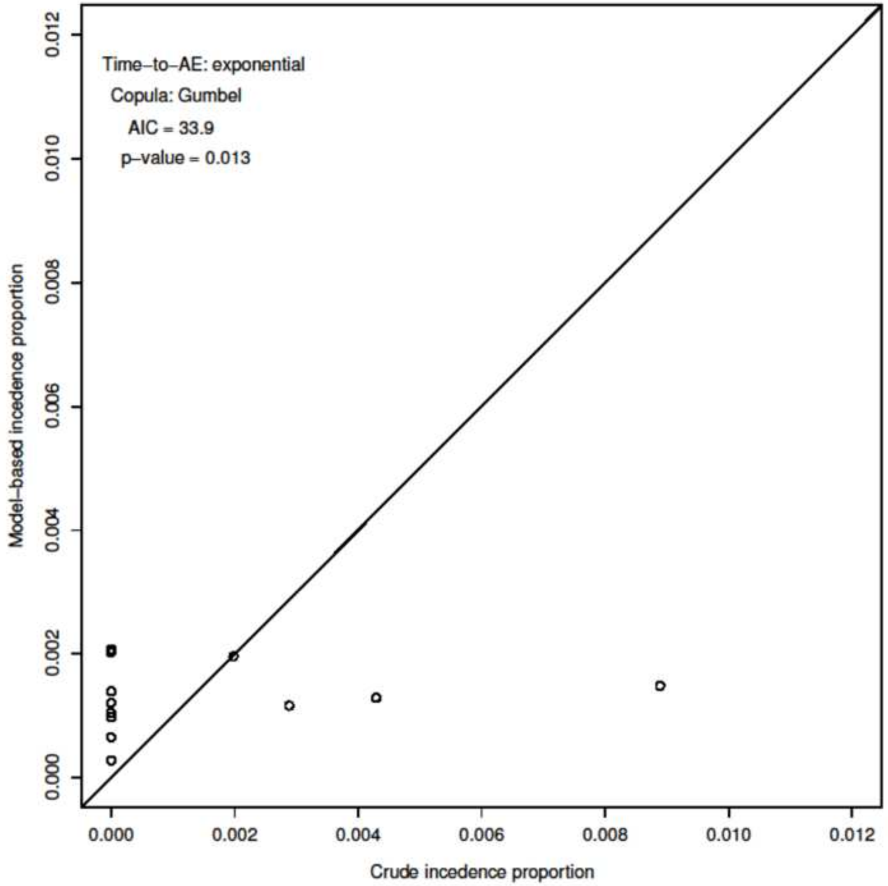


Application to motivating data:
under dependent follow-up

BV group



CT group



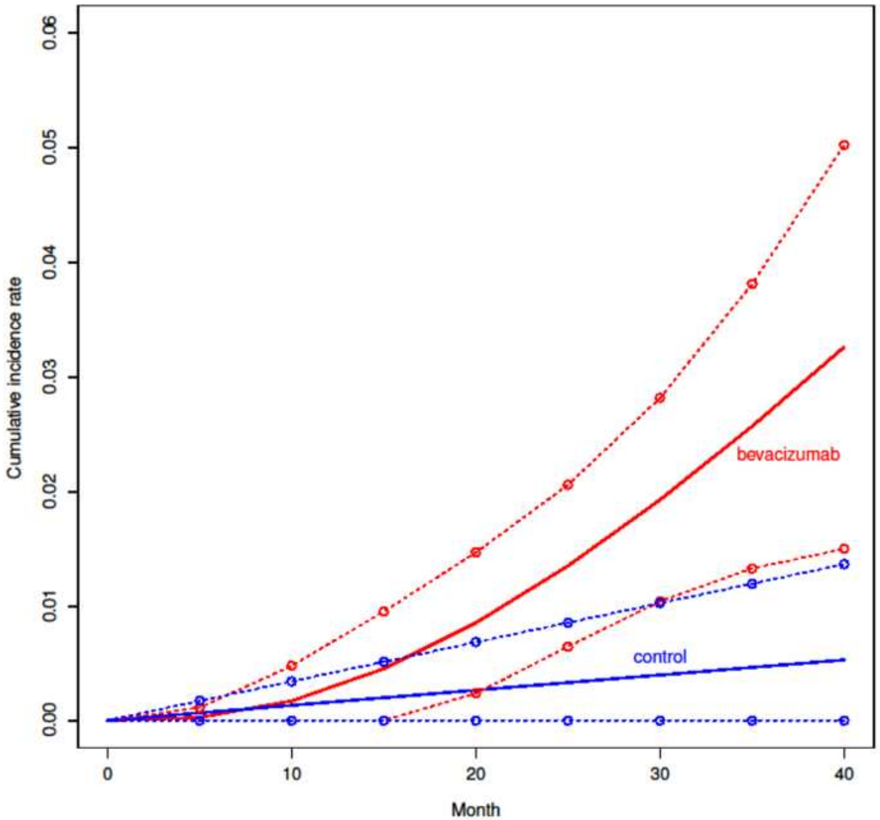
Model-based incidence proportion

Crude incidence proportion

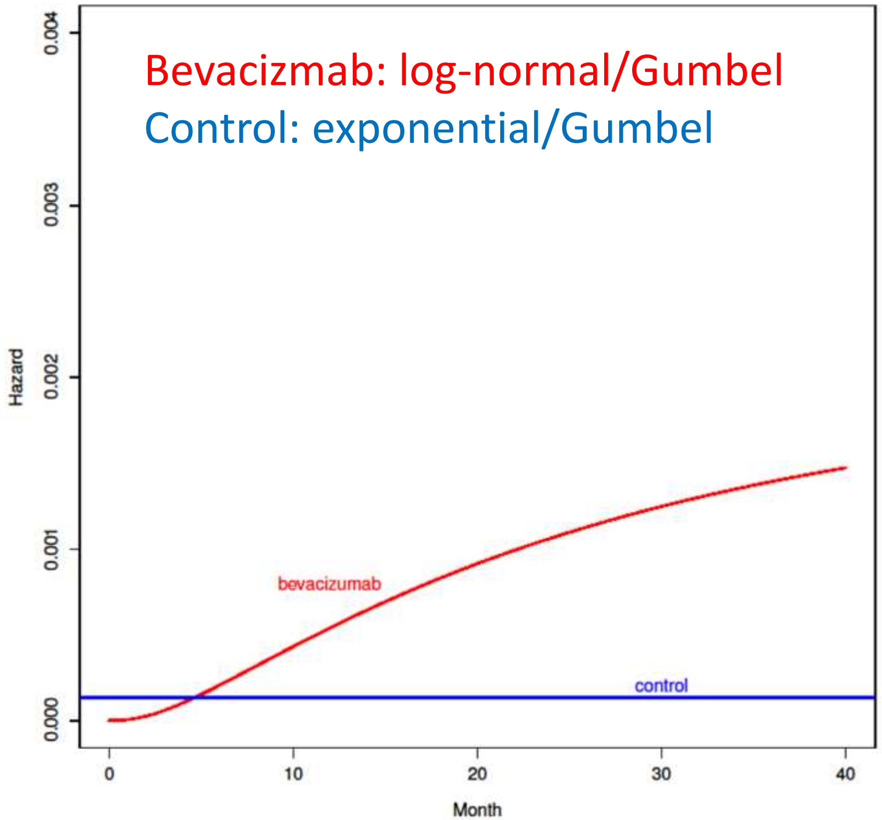
Crude incidence proportion

Application to real data: under dependent follow-up

$P\left(T_{k,i}^{(s)\,AE} \le t : \hat{\theta}_k\right)$
with the best model w.r.t AIC



Hazard function



Application to motivating data

	Independent		Dependent	
t	RR (95%CI)	P-value	RR (95%CI)	P-value
5	1.404(0.134,14.738)	0.777	0.394(0.010,15.183)	0.617
10	3.178(0.860,11.739)	0.083	1.289(0.118,14.089)	0.835
15	4.664(1.835,11.854)	0.001	2.273(0.331,15.633)	0.404
20	5.875(2.581,13.377)	<0.001	3.215(0.566,18.271)	0.188
25	6.865(2.998,15.720)	<0.001	4.077(0.772,21.530)	0.098
30	7.679(3.197,18.443)	<0.001	4.851(0.936,25.128)	0.060
35	8.354(3.282,21.268)	<0.001	5.540(1.063,28.870)	0.042
40	8.918(3.308,24.041)	<0.001	6.153(1.160,32.619)	0.033

Simulation study(S=13): Setting of data generation

Study-level data:
- Mimicking S=13 studies in Zuo et al. (2014)
- Same sample size of each 13 studies
- Only BV group (k=1)

Individual patient data:

$T_{k,i}^{(s)} \sim EX\left(\lambda^{(s)}\right)$ $\lambda^{(s)}$ was determined by MST in Zuo et al. (2014)

$T_{k,i}^{(s)AE} \sim EX\left(\lambda_k^{AE}\right)$ λ^{AE}: 3 scenarios were considered.

$C_{k,i}^{(s)} \sim EX\left(\lambda_C^{(s)}\right)$ $\lambda_C^{(s)}$ was randomly assigned.

Generate IPD and then create 1,000 sets of aggregated data under (1) Independent follow-up (2)dependent follow-up

Simulation study(S=13): Setting of data generation

$\lambda_k^{(s)}$ was determined by MST in Zuo et al. (2014)

λ_k^{AE}: 3 scenarios were considered.

λ_k^{C} was randomly assigned.

study	Authors	n	Median PFS	$\lambda^{(s)}$	$\lambda_C^{(s)}$
1	Aghajanian, 2012	242	12.4	0.0243	0.02
3-1	Burger, 2011	625	11.2	0.0269	0.015
3-2	Burger, 2011	623	14.1	0.0213	0.015
4	Chinot, 2014	458	10.6	0.0284	0.025
5-1	Giantonio, 2007	237	2.7	0.1115	0.01
5-2	Giantonio, 2007	280	7.3	0.0412	0.015
6	Herbst, 2011	319	3.4	0.0885	0.018
8	Kelly, 2012	524	9.9	0.0304	0.02
9	Kim, 2012	143	5.6	0.0538	0.012
11	Kindler, 2010	300	3.8	0.0792	0.01
12	Miller, 2007	347	11.8	0.0255	0.024
14	Perren, 2011	764	19.8	0.0152	0.015
17	Sandler, 2006	417	6.2	0.0486	0.01

Simulation study: Setting of data generation

$\lambda_k^{(s)}$ was determined by MST in Zuo et al. (2014)

λ_k^{AE}: 3 scenarios were considered.

λ_k^{C} was randomly assigned.

Scenario1

$\lambda_k^{AE} = 0.2 \times 10^{-2}$, empirical incidence proportion: 0.023

Scenario2

$\lambda_k^{AE} = 1 \times 10^{-2}$, empirical incidence proportion: 0.116

Scenario3

$\lambda_k^{AE} = 5 \times 10^{-2}$, empirical incidence proportion: 0.556

Simulation study: Setting of data generation

(1) Independent follow-up

(2) Dependent follow-up

Copula C_{ψ_k}: Frank, Clayton, Gumbel

Two parameter settings for ψ_k

- low dependence: Kendall tau=0.2
- Moderate dependent: Kendall tau=0.5

Simulation study: Applied methods

Model for $T_{k,i}^{(s)AE}$: exponential (correctly specified)

Copula C_{ψ_k}: independent, Frank, Clayton, Gumbel

Select the best Copula via AIC

Simulation study(S=13):

Results for dataset generated under independent follow-up

	Data		Model			
Parameter	Scenario	True	Independent	Frank	Clayton	Gumbel
$100 \times \lambda_{AE}$	1	0.2	0.199 (0.187, 0.212)	0.158 (0.068, 0.582)	0.224 (0.199, 0.302)	0.238 (0.203, 0.518)
median (q1/q3)	2	1	0.998 (0.968, 1.026)	1.006 (0.739, 1.267)	1.038 (0.993, 1.134)	1.060 (1.006, 1.317)
	3	5	4.980 (4.899, 5.062)	4.994 (4.843, 5.139)	5.041 (4.946, 5.153)	5.102 (5.014, 5.216)
CP (NoC)	1	0.95	0.960 (960)	0.735 (546)	0.976 (911)	0.974 (526)
	2	0.95	0.975 (975)	0.890 (884)	0.976 (959)	0.948 (494)
	3	0.95	0.983 (983)	0.987 (987)	0.977 (959)	0.969 (818)
Selected by AIC	1		790	144	39	27
	2		832	91	38	39
	3		857	68	26	49

If correct independent model was fit, exponential hazard for AE was well estimated.

Extra dependence model did not lead poor performance for scenarios 2 and 3.
It could give poor estimates for scenario 1 (rare event case) .
Frank copula might give conservative CP.

AIC selected the true independent structure frequently.

Simulation study(S=13):
Results for dataset generated under dependent follow-up

median (q1/q3)

Parameter	scn.	TRUE	dep.	ψ_k	Independent	Frank	Clayton	Gumbel
$100 \times \lambda_{AE}$	1	0.2	Frank	1.87	0.288 (0.274, 0.303)	0.206 (0.098, 0.523)	0.283 (0.255, 0.369)	0.270 (0.171, 0.507)
				5.75	0.427 (0.410, 0.445)	0.225 (0.153, 0.483)	0.440 (0.418, 0.482)	0.447 (0.424, 0.513)
			Clayton	0.5	0.063 (0.056, 0.070)	0.064 (0.022, 0.620)	0.207 (0.100, 0.348)	0.531 (0.128, 1.034)
				2	0.002 (0.000, 0.002)	0.000 (0.000, 0.001)	0.045 (0.038, 0.939)	0.001 (0.000, 1.472)
			Gumbel	1.25	0.124 (0.114, 0.133)	0.127 (0.044, 0.689)	0.151 (0.125, 0.245)	0.187 (0.129, 0.555)
				2	0.038 (0.032, 0.044)	0.027 (0.011, 0.196)	0.066 (0.039, 0.182)	0.131 (0.042, 0.611)
	2	1	Frank	1.87	1.325 (1.291, 1.359)	0.998 (0.771, 1.243)	1.263 (1.220, 1.326)	1.024 (0.864, 1.257)
				5.75	1.730 (1.695, 1.768)	1.018 (0.925, 1.218)	1.657 (1.601, 1.710)	1.754 (1.720, 1.792)
			Clayton	0.5	0.581 (0.560, 0.603)	1.476 (1.211, 1.750)	0.984 (0.861, 1.114)	1.549 (1.250, 1.808)
				2	0.092 (0.084, 0.101)	2.303 (0.073, 2.548)	0.982 (0.768, 1.228)	2.077 (1.703, 2.446)
			Gumbel	1.25	0.687 (0.661, 0.711)	0.932 (0.613, 1.200)	0.787 (0.708, 0.901)	0.946 (0.719, 1.257)
				2	0.280 (0.266, 0.295)	0.991 (0.473, 1.485)	0.494 (0.378, 0.612)	0.912 (0.559, 1.251)
	3	5	Frank	1.87	5.451 (5.364, 5.535)	5.029 (4.871, 5.163)	5.474 (5.387, 5.558)	4.948 (3.047, 5.206)
				5.75	5.890 (5.817, 5.964)	5.034 (4.920, 5.170)	5.914 (5.840, 5.990)	5.978 (5.902, 6.056)
			Clayton	0.5	4.401 (4.329, 4.490)	5.050 (4.919, 5.170)	4.991 (4.865, 5.116)	5.109 (4.974, 5.238)
				2	3.028 (2.970, 3.093)	5.110 (4.996, 5.225)	4.971 (4.857, 5.101)	5.180 (5.064, 5.294)
			Gumbel	1.25	4.326 (4.240, 4.407)	4.917 (4.793, 5.045)	4.848 (4.723, 4.970)	5.002 (4.870, 5.130)
				2	3.103 (3.034, 3.177)	4.862 (4.734, 4.978)	4.638 (4.511, 4.759)	4.983 (4.863, 5.100)

If event rate was moderate or high (scenario 2 or 3), correctly specified Copula provided unbiased estimates of exponential hazard for AE.
For rare events (scenario 1), there might be biases even with correctly specified Copula.
Misspecified copula gave biased estimates.

Correctly specified case

Simulation study(S=13):
Results for dataset generated under dependent follow-up

Parameter	scn.	TRUE	dep.	ψ_k	Independent	Frank	Clayton	Gumbel
CP(NoC)	1	0.95	Frank	1.87	0.021 (21)	0.752 (629)	0.975 (890)	0.880 (863)
				5.75	0.000 (0)	0.828 (749)	0.239 (231)	0.862 (301)
			Clayton	0.5	0.000 (0)	0.525 (264)	0.928 (894)	0.785 (711)
				2	0.000 (0)	0.713 (62)	0.903 (660)	0.900 (242)
			Gumbel	1.25	0.003 (3)	0.666 (411)	0.638 (560)	0.935 (571)
				2	0.000 (0)	0.694 (227)	0.834 (563)	0.898 (538)
	2	0.95	Frank	1.87	0.000 (0)	0.856 (853)	0.937 (921)	0.937 (937)
				5.75	0.000 (0)	0.919 (899)	0.015 (15)	0.046 (9)
			Clayton	0.5	0.000 (0)	0.812 (811)	0.977 (963)	0.000 (0)
				2	0.000 (0)	0.174 (130)	0.962 (962)	0.519 (519)
			Gumbel	1.25	0.000 (0)	0.890 (885)	0.718 (712)	0.935 (662)
				2	0.000 (0)	0.840 (795)	0.306 (302)	0.957 (833)
	3	0.95	Frank	1.87	0.188 (188)	0.992 (990)	0.138 (137)	0.680 (602)
				5.75	0.000 (0)	0.997 (968)	0.002 (2)	0.000 (0)
			Clayton	0.5	0.013 (13)	0.961 (961)	0.978 (978)	0.923 (923)
				2	0.000 (0)	0.815 (815)	0.892 (892)	0.647 (647)
			Gumbel	1.25	0.003 (3)	0.970 (970)	0.947 (947)	0.980 (980)
				2	0.000 (0)	0.861 (861)	0.456 (456)	0.913 (913)

If event rate was moderate or high (scenario 2 or 3), correctly specified Copula provided Proper CPs in most cases.

If event rate was small (scenario 1), CP could be anti-conservative.

Simulation study(S=13):
Results for dataset generated under dependent follow-up

Parameter	scn.	TRUE	dep.	ψ_k	Independent	Frank	Clayton	Gumbel
Selected by AIC	1		Frank	1.87	792	101	40	67
				5.75	792	169	31	8
			Clayton	0.5	552	67	196	185
				2	382	51	425	142
			Gumbel	1.25	774	115	59	52
				2	753	80	106	61
	2		Frank	1.87	687	231	5	77
				5.75	271	728	1	0
			Clayton	0.5	182	178	486	154
				2	2	9	740	249
			Gumbel	1.25	742	94	90	74
				2	471	158	256	115
	3		Frank	1.87	157	679	0	164
				5.75	0	1,000	0	0
			Clayton	0.5	16	156	552	276
				2	0	137	832	31
			Gumbel	1.25	50	155	246	549
				2	0	262	74	664

AIC did not select the correct model frequently.
It likely selected independent copula when event rate was low (scenario 1).

Summary of simulation study

We also conducted a simulation study with S=30.
Some issues observed with the case of S=13 did not matter with S=30.

Independent follow-up case:
- The proposed method with independent Copula had negligible biases and proper CPs.
- Unnecessary specification of dependent Copula might lead biases and poor CPs when the hazard of AE was small.

Dependent follow-up case:
- If the hazard of AE was NOT small, the proposed method with correctly specified Copula had negligible biases and proper CPs.
- If the hazard of AE was small, it did NOT hold.
- If Copula was misspecified, biased estimates were obtained.

Summary

We proposed a method to estimate the survival function for the time-to-AE based on regularly reported empirical incidence proportion of AE and Kaplan-Meier for the primary time-to-event endpoint.

Unless the hazard of AE is extremely low, our method works well.

Incidence proportion is a simple and useful measure for the analysis of AE.
Care for heterogeneous follow-up durations should be made in discussing risk-benefit trade-off among several treatments.

Future work

The proposed method assumes the survival function of the time-to-AE was common across studies.
It is important to evaluate heterogeneity among studies.
- Incorporating frailty in AE survival distributions.

Some improvement should be made in case of small hazard of AE.

Bayesian methods or penalized methods would be helpful for these issues.

Thank you so much for your kind attention!

Simulation study(S=30):
Results for dataset generated under independent follow-up

Parameter	Scenario	TRUE	Independent	Frank	Clayton	Gumbel
$100 \times \lambda_{AE}$	1	0.2	0.200 (0.192, 0.208)	0.210 (0.109, 0.389)	0.209 (0.180, 0.259)	0.227 (0.154, 0.354)
	2	1	0.996 (0.976, 1.018)	0.996 (0.875, 1.120)	0.995 (0.943, 1.071)	1.029 (0.894, 1.170)
median (q1/q3)	3	5	4.966 (4.902, 5.028)	4.998 (4.917, 5.082)	5.018 (4.944, 5.099)	5.062 (4.988, 5.145)
CP(NoC)	1	0.95	0.970 (970)	0.799 (661)	0.983 (894)	0.875 (870)
	2	0.95	0.964 (964)	0.956 (956)	0.989 (974)	0.928 (928)
	3	0.95	0.963 (963)	0.987 (987)	0.978 (963)	0.962 (962)
Selected by AIC	1		762	85	47	106
	2		729	76	28	167
	3		762	45	15	179

If correct independent model was fit, exponential hazard for AE was well estimated.

Extra dependence model did not lead poor performance for scenarios 2 and 3.
It could give poor estimates for scenario 1 (rare event case) .
Frank copula might give conservative CP.

AIC selected the true independent structure frequently.

Simulation study(S=30):
Results for dataset generated under dependent follow-up

median (q1/q3)

Parameter	scn.	TRUE	dep.	ψ_k	Independent	Frank	Clayton	Gumbel
$100 \times \lambda_{AE}$	1	0.2	Frank	1.87	0.287 (0.277, 0.298)	0.233 (0.138, 0.382)	0.274 (0.255, 0.324)	0.276 (0.206, 0.381)
				5.75	0.419 (0.407, 0.431)	0.251 (0.178, 0.364)	0.392 (0.374, 0.421)	0.342 (0.287, 0.419)
			Clayton	0.5	0.071 (0.066, 0.076)	0.303 (0.045, 0.948)	0.196 (0.144, 0.257)	0.473 (0.289, 0.666)
				2	0.002 (0.001, 0.003)	0.001 (0.000, 0.007)	0.239 (0.037, 0.625)	0.474 (0.014, 1.092)
			Gumbel	1.25	0.126 (0.119, 0.132)	0.186 (0.072, 0.429)	0.138 (0.113, 0.183)	0.193 (0.105, 0.349)
				2	0.040 (0.037, 0.044)	0.037 (0.014, 0.220)	0.071 (0.039, 0.120)	0.137 (0.036, 0.340)
	2	1	Frank	1.87	1.294 (1.271, 1.318)	1.015 (0.895, 1.127)	1.236 (1.206, 1.274)	1.089 (1.002, 1.186)
				5.75	1.654 (1.630, 1.678)	1.018 (0.950, 1.116)	1.600 (1.564, 1.627)	1.223 (1.149, 1.295)
			Clayton	0.5	0.624 (0.609, 0.639)	1.265 (1.153, 1.380)	0.978 (0.913, 1.051)	1.377 (1.246, 1.498)
				2	0.138 (0.131, 0.144)	2.205 (2.006, 2.371)	0.984 (0.881, 1.074)	1.760 (1.628, 1.889)
			Gumbel	1.25	0.703 (0.686, 0.720)	0.937 (0.805, 1.057)	0.821 (0.747, 0.886)	0.989 (0.834, 1.117)
				2	0.306 (0.296, 0.318)	0.943 (0.767, 1.121)	0.545 (0.472, 0.615)	0.931 (0.757, 1.088)
	3	5	Frank	1.87	5.283 (5.225, 5.345)	5.011 (4.923, 5.091)	5.472 (5.398, 5.576)	5.101 (5.017, 5.182)
				5.75	5.573 (5.517, 5.631)	5.011 (4.931, 5.103)	5.011 (4.931, 5.103)	5.143 (5.051, 5.234)
			Clayton	0.5	4.568 (4.509, 4.627)	5.006 (4.932, 5.078)	5.155 (4.989, 7.825)	5.053 (4.981, 5.126)
				2	3.586 (3.532, 3.633)	5.001 (4.937, 5.066)	5.006 (4.938, 5.074)	5.018 (4.954, 5.083)
			Gumbel	1.25	4.519 (4.456, 4.579)	4.999 (4.920, 5.065)	5.113 (4.965, 7.672)	5.049 (4.969, 5.113)
				2	3.664 (3.610, 3.723)	5.001 (4.938, 5.065)	4.987 (4.921, 5.055)	5.029 (4.967, 5.090)

If event rate was moderate or high (scenario 2 or 3), correctly specified Copula provided unbiased estimates of exponential hazard for AE.
For rare events (scenario 1), there might be biases even with correctly specified Copula.
Misspecified copula gave biased estimates.

Correctly specified case

Simulation study(S=30):
Results for dataset generated under dependent follow-up

Parameter	scn.	TRUE	dep.	ψ_k	Independent	Frank	Clayton	Gumbel
CP(NoC)	1	0.95	Frank	1.87	0.000 (0)	0.859 (801)	0.932 (838)	0.955 (953)
				5.75	0.000 (0)	0.899 (881)	0.377 (320)	0.973 (973)
			Clayton	0.5	0.000 (0)	0.608 (454)	0.976 (973)	0.809 (781)
				2	0.000 (0)	0.622 (97)	0.924 (645)	0.815 (564)
			Gumbel	1.25	0.000 (0)	0.760 (567)	0.942 (853)	0.826 (796)
				2	0.000 (0)	0.564 (285)	0.770 (689)	0.760 (600)
	2	0.95	Frank	1.87	0.000 (0)	0.938 (938)	0.646 (629)	0.976 (976)
				5.75	0.000 (0)	0.930 (920)	0.000 (0)	0.835 (833)
			Clayton	0.5	0.000 (0)	0.644 (644)	0.954 (954)	0.494 (494)
				2	0.000 (0)	0.019 (15)	0.933 (933)	0.032 (32)
			Gumbel	1.25	0.000 (0)	0.963 (963)	0.603 (602)	0.937 (937)
				2	0.000 (0)	0.945 (936)	0.015 (15)	0.940 (940)
	3	0.95	Frank	1.87	0.260 (260)	0.996 (996)	0.018 (17)	0.962 (962)
				5.75	0.000 (0)	0.992 (968)	0.992 (968)	0.954 (954)
			Clayton	0.5	0.019 (19)	0.969 (969)	0.910 (518)	0.946 (946)
				2	0.000 (0)	0.853 (853)	0.834 (834)	0.848 (848)
			Gumbel	1.25	0.001 (1)	0.963 (963)	0.938 (546)	0.943 (924)
				2	0.000 (0)	0.891 (891)	0.880 (880)	0.875 (875)

If event rate was moderate or high (scenario 2 or 3), correctly specified Copula provided Proper CPs in most cases.

If event rate was small (scenario 1), CP could be anti-conservative.

Simulation study(S=30):
Results for dataset generated under dependent follow-up

Parameter	scn.	TRUE	dep.	ψ_k	Independent	Frank	Clayton	Gumbel
Selected by AIC	1		Frank	1.87	783	90	15	111
				5.75	656	218	10	116
			Clayton	0.5	278	104	426	192
				2	435	41	328	203
			Gumbel	1.25	724	107	50	119
				2	624	121	130	125
	2		Frank	1.87	334	485	7	174
				5.75	4	946	4	50
			Clayton	0.5	8	136	617	239
				2	0	1	908	91
			Gumbel	1.25	472	115	138	275
				2	81	239	436	244
	3		Frank	1.87	2	701	0	297
				5.75	0	871	0	129
			Clayton	0.5	0	207	478	315
				2	0	200	775	25
			Gumbel	1.25	0	274	69	657
				2	0	157	3	840

AIC was likely to select the true dependence structure when event rate was not low.
It likely selected independent copula when event rate was low (scenario 1).