Risk reduction derived from the Cox proportional hazard model
– A simulation study using real-world data –

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Background

- "Cox proportional hazard model" ("Cox") with a binary covariate is widely used to assess the effect of intervention (I) on cardiovascular event risks.
- When hazard ratio (HR)<1, the risk reduction (RR) is often interpreted as "(1 – HR) × 100[%]".
- "('1 – cumulative survival rates[S(t)]' ('cumulative incidence [CuI]') for control(C) – CuI for I) × 100[%]" is easy to understand as RR.
- However, the HR interpretation and the difference in CuI are different.
- This study investigated the optimal method for calculating the real RR using HR and the difference in CuI.

Research design & Methods

- We analyzed glucose levels (GL) for 100 outpatients with Type 2 diabetes, measured by CGM (FreeStyle Libre Pro) over 24-h for 13 days.
- S(t) was analyzed using Cox[S(t)Cox] and Kaplan-Meier (KM) method[S(t)KM] for 30 time-to-event endpoints where time to event was expected to be delayed by I, compared to C. Observations were done at all GL measurement.
- "{(1 – S(t)Cox for C) – (1 – S(t)Cox for I)} × 100" ("CoxRR") and "{(1 – S(t)KM for C) – (1 – S(t)KM for I)} × 100" ("KMRR") were calculated.
- A new metric, Adjusted RR, was proposed using the formula for meta-analytic risk ratio proposed in Cochrane Handbook, "(1 – risk ratio) × total incidence for C(%C)". This formula approximates "(1 – total incidence for I (%I) ÷ %C) × %C=%C – %I".

  If %C is changed to –Loge(S(t)Cox for C)(−LN[S(t)Cox]C) and %I is changed to –Loge(S(t)Cox for I) (−LN[S(t)Cox]I), the formula becomes "(1 – '−LN[S(t)Cox]I ÷ LN[S(t)Cox]C'['HR']) × −LN[S(t)Cox]C=−LN[S(t)Cox]C − −LN[S(t)Cox]I".

  First, S(t)KM for C is logarithmically transformed to –Loge(S(t)KM for C) (−LN[S(t)KM]C).

  Second, when −LN[S(t)KM]C is substituted for −LN[S(t)Cox]C, (1 – HR) × −LN[S(t)KM]C indicates −LN[S(t)KM]C − adjusted−LN[S(t)KM]I.

  Third, the adjusted−LN[S(t)KM]I is exponentially transformed to adjusted[S(t)KM]I.

  Fourth, "{(1 – [S(t)KM]C) – (1 – adjusted[S(t)KM]I)} × 100" was proposed as Adjusted RR.

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> Primary endpoints

  The difference between |CoxRR – Adjusted RR| and |CoxRR – KMRR|

Results

Characteristic	Values
N (Male / Female)	100 (60 / 40)
Age, years	69.5 ± 13.4
BMI, kg/m^2	24.2 ± 4.1
HbA1c, %	8.0 ± 1.5

Baseline characteristics
Data are shown as median (interquartile range).
BMI, body mass index; HbA1c, hemoglobin A1c

TBR, time below range; CV, coefficient of variation; GRI[1], Glycemia risk index; BGI[2]: blood glucose index; Mean, mean glucose level; SD, standard deviation; HBGI[2]: high blood glucose index; HI[3], Hyperglycemic index; J index[4], J index; Median, median glucose level

1, Klonoff DC, et al. J Diabetes Sci Technol. 2023;17: 1226-1242.
2, Kovatchev B. J Diabetes Sci Technol. 2019; 13: 627-635.
3, Rodbard D. Diabetes Technol Ther. 2009; 11: 551-565.
4, Wójcicki JM. Horm Metab Res. 1995; 27: 41-42.

The metrics for the 30 outcomes

Outcome	Intervention/Control	HR	CoxRR, %	Adjusted RR, %	KMRR, %	|CoxRR - Adjust RR|	|CoxRR - KMRR|
First time of <70 mg/dL	HbA1c>8%/HbA1c<8%	0.27	40.88	41.07	41.09	0.18	0.20
First time of <60 mg/dL	HbA1c>8%/HbA1c<8%	0.11	41.53	42.03	42.15	0.50	0.62
First time of >250 mg/dL	HbA1c<8%/HbA1c>8%	0.40	21.81	19.85	22.24	1.96	0.42
First time of >300 mg/dL	HbA1c<8%/HbA1c>8%	0.30	41.99	42.22	35.78	0.23	6.21
First time of >250 mg/dL	CV<30%/CV>30%	0.86	4.41	3.99	8.23	0.42	3.82
First time of >300 mg/dL	CV<30%/CV>30%	0.55	21.48	21.49	25.41	0.02	3.94
Achievement of time above 180 mg/dL>25% of 13 days	HbA1c<8%/HbA1c>8%	0.23	47.59	48.22	45.08	0.63	2.51
Achievement of time above 250 mg/dL>5% of 13 days	HbA1c<8%/HbA1c>8%	0.21	50.52	49.43	46.35	1.09	4.17
First time of <70 mg/dL	BMI>24/BMI<24	0.63	15.38	15.67	18.28	0.28	2.89
First time of <70 mg/dL	Age<70/Age>70	0.52	21.74	21.96	22.91	0.22	1.16
Achievement of TBR<70>1% of 13 days	Age<70/Age>70	0.30	28.81	29.29	29.89	0.48	1.07
Achievement of TBR<70>1% of 13 days	BMI>24/BMI<24	0.44	21.03	21.51	22.71	0.48	1.67
Achievement of time out of 70-180 mg/dL>30% of 13 days	Age<70/Age>70	0.78	8.89	8.90	9.03	0.01	0.14
Achievement of TBR<70>4% of 13 days	Age<70/Age>70	0.42	14.01	14.04	13.96	0.03	0.05
Achievement of TBR<70>4% of 13 days	BMI>24/BMI<24	0.49	11.96	12.25	12.88	0.29	0.92
Achievement of TBR<54>1% of 13 days	Age<70/Age>70	0.22	15.57	15.80	15.93	0.23	0.36
Achievement of TBR<54>1% of 13 days	BMI>24/BMI<24	0.65	5.45	5.53	5.80	0.08	0.35
First time of >250 mg/dL	GRI<36/GRI>36	0.34	25.75	29.02	22.00	3.27	3.75
First time of >300 mg/dL	GRI<36/GRI>36	0.16	59.35	59.46	58.00	0.11	1.35
First time of >300 mg/dL	BGI<7.5/BGI>7.5	0.13	63.33	63.90	61.54	0.57	1.79
Achievement of time out of 70-180 mg/dL>30% of 13 days	GRI<36/GRI>36	0.07	73.22	75.16	68.00	1.93	5.22
Achievement of time out of 54-250 mg/dL>6% of 13 days	GRI<36/GRI>36	0.05	79.40	78.81	78.00	0.59	1.40
Achievement of time out of 54-250 mg/dL>6% of 13 days	BGI<7.5/BGI>7.5	0.03	86.29	86.06	84.42	0.23	1.87
First time of >300 mg/dL	Mean<160/Mean>160	0.20	53.13	53.18	50.00	0.05	3.13
First time of >300 mg/dL	SD<50/SD>50	0.12	64.36	63.41	65.56	0.96	1.19
First time of >300 mg/dL	HBGI<7/HBGI>7	0.12	64.52	65.62	61.54	1.10	2.98
First time of >300 mg/dL	HI<2.5/HI>2.5	0.05	80.08	80.40	80.83	0.31	0.75
First time of >300 mg/dL	J index<45/J index>45	0.12	65.39	65.54	64.47	0.14	0.93
First time of >300 mg/dL	Median<155/Median>155	0.20	54.03	54.10	52.46	0.07	1.57
Achievement of time above 250 mg/dL>5% of 13 days	Mean<160/Mean>160	0.08	69.89	69.00	68.00	0.90	1.89

> HR was <1 in the 30 outcomes.
> |CoxRR – Adjusted RR| was significantly lower than |CoxRR – KMRR|.

p: paired t-test 0.6% vs 1.9%, p<0.001

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Conclusion

> Adjusted RR may more accurately reflect actual RR than KMRR.