Ideal automation for insulin management – with interpretation of risk ratio

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Using device-supported automated basal insulin (BI) titration was reported to be associated with reducing HbA1c.[1] In *The Lancet Regional Health-Western Pacific*, a meta-analysis of randomized controlled trials (RCTs) by Luo, Chang et al. confirmed the association between using automated BI titration and HbA1c level reduction as automated management is more accurate than self-management.[2] However, patient self-titration was more effective than practitioner-led titration in terms of non-influence by doctors' clinical inertia and better patient engagement.[3–5] Overall, automation promoting not clinical inertia but motivation is ideal for insulin management.

In Chang's report, the Cochran–Mantel–Haenszel test was used to analyze the common risk ratio. The meta-analysis including three RCTs revealed that the proportion of people reaching the target of HbA1c level<7% is significantly higher with automated BI titration [intervention] than with conventional care [control] (risk ratio (RR), 1.82 [95% confidence interval (CI), 1.16–2.86]). Thus, the "target incidence for intervention [%]" (%I) was 1.82 times higher than that of the "target incidence for control [%]" (%C). In a previous meta-analysis report, when the RR was 1.37, the RR was interpreted as "having a 37% higher risk".[6] In this case, if %I and %C are interchanged, the RR becomes 1 ÷ 1.37≈0.73. Then, the RR was interpreted as "having a 27% lower risk". The percentage of risk reduction by intervention should be calculated by "%C – %I". In the Cochrane handbook, the risk difference in percentage is proposed as "%C × (1 – RR)".[7] This may be because "%C × (1 – %I ÷ %C) = %C – %I". In the Cochran–Mantel–Haenszel test, common RR (CRR) ≈ total %I ÷ total %C, but not = , owing to adjustment. In the risk difference in percentage, if %I and %C are interchanged, "%I × (1 – %C ÷ %I) = %I – %C", which is reasonable. Readers can calculate the risk difference in percentage from the RR and total %C. Chang's report is excellent in terms of not using misleading expressions.

This issue regarding the ratio is applicable to the hazard ratio (HR) analyzed using the Cox proportional hazard model with a "binary covariate" (BC). When the BC is 1 for intervention and 0 for control, $-\log_e S(t)$ for intervention (–LN[S(t)]I) ÷ $-\log_e S(t)$ for control (–LN[S(t)]C) = HR [S(t) = cumulative survival rate function]. In the formula of risk difference in percentage, "%C × (1 – %I ÷ %C)", if %C is changed to –LN[S(t)]C and %I is changed to –LN[S(t)]I, the formula becomes "–LN[S(t)]C × (1 – '–LN[S(t)]I ÷ –LN[S(t)]C' ['HR']". Thus, firstly, "cumulative survival rate for Kaplan–Meier method" (S(t)KM) estimated from the KM curve for control in reports is logarithmically transformed to –LN[S(t)KM]C. Secondly, because "–LN[S(t)KM]C × (1 – HR)" indicates "–LN[S(t)KM]C – adjusted –LN[S(t)KM]I," an adjusted –LN[S(t)KM]I can be calculated. Third, the adjusted –LN[S(t)KM]I is exponentially transformed to adjusted [S(t)KM]I. Finally, {(1 – [S(t)KM]C) – (1 – adjusted [S(t)KM]I)} × 100 indicates the "risk difference in percentage adjusted by HR [%]" (RD %aHR). Using this method, the percentage of risk reduction considering the time axis can be estimated theoretically. However, high credibility of HR is needed to guarantee the accuracy of RD%aHR. For example, increased censoring and a biased ratio of intervention to control can theoretically reduce the credibility of HR. However, the credibility of difference between [S(t)KM]C and [S(t)KM]I decreases more than that of HR. Thus, RD%aHR should be used in cases with more censoring.

In a previous report assessing the relationship between HbA1c and time-to-death using a Cox model, various HbA1c (1 of BC) was compared to HbA1c7.5% (0 of BC).[8] In which case, comparing the magnitude relationship of HR is meaningful because censoring biases are relatively common. Moreover, a report regarding side effects evidences that lower event incidences led to a wider 95%CI of ratio.[9] Credibility of ratio should be interpreted considering event incidences.

The ratio of intervention to control may theoretically affect the credibility of HR. In a previous report, for stroke events in diabetic patients, the 95%CI of HR, when depressive symptoms and moderate/severe stress ("DandS") = 1 and non-symptoms = 0 in BC, is wider than that, when depressive symptoms or moderate/severe stress ("DorS") = 1 and non-symptoms = 0, despite similar HR.[10] The n of DandS (416) was lower than that of DorS (1091), and the n of non-symptoms was 2583. A lower ratio of DandS to non-symptoms may cause a wider 95%CI of HR. Credibility of HR should be interpreted by referring to the ratio of intervention to control. Although event incidences cannot be predicted,

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the ratio of intervention to control is human-caused, which should be recognized as an issue.

Chang's report revealed the importance of automation promoting not clinical inertia but motivation for insulin management, with appropriate statistical interpretation. Further improvements in the quality of insulin management and statistical interpretation are required.

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Declaration of interests

None of the authors has any relevant conflicts of interest to disclose.

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References

1 Franc S, Joubert M, Daoudi A, et al. Efficacy of two telemonitoring systems to improve glycaemic control during basal insulin initiation in patients with type 2 diabetes: the TeleDiab- 2 randomized controlled trial. *Diabetes Obes Metabol*. 2019;21(10):2327–2332.

2 Luo Y, Chang Y, Zhao Z, et al. Device-supported automated basal insulin titration in adults with type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials. *Lancet Reg Health West Pacific*. 2023;35:100746. https://doi.org/10.1016/j.lanwpc.2023.100746.

3 Khunti K, Millar-Jones D. Clinical inertia to insulin initiation and intensification in the UK: a focused li terature review. *Primary Care Diabetes*. 2017;11(1):3–12.

4 Huckvale K, Adomaviciute S, Prieto JT, Leow MK, Car J. Smartphone apps for calculating insulin dose: a systematic assessment. *BMC Med*. 2015;13(1):106.

5 Godinho MA, Jonnagaddala J, Gudi N, Islam R, Narasimhan P, Liaw ST. mHealth for integrated people centred health services in the Western Pacific: a systematic review. *Int J Med Inf*. 2020;142(1):104259.

6 Soteriades ES, Kim J, Christophi CA, Kales SN. Cancer incidence and mortality in firefighters: a state-of-the-art review and meta-.Analysis. *Asian Pac J Cancer Prev*. 2019;20(11):3221–3231

7 Higgins JPT, Thomas J, Chandler J, et al. *Cochrane handbook for systematic reviews of interventions*. 2nd ed. Chichester (UK): John Wiley & Sons; 2019.

8 Currie CJ, Peters JR, Tynan A. Survival as a function of HbA(1c) in people with type 2 diabetes: a retrospective cohort study. *Lancet*. 2010;375(9713):481–489.

9 Arai M, Shirakawa J, Konishi H, Sagawa N, Terauchi Y. Bullous pemphigoid and dipeptidyl peptidase 4 inhibitors: a disproportionality analysis based on the Japanese Adverse Drug Event Report Database. *Diabetes Care*. 2018;41(9):e130–e132.

10 Cummings DM, Kirian K, Howard G, et al. Consequences of comorbidity of elevated stress and/or depressive symptoms and incident cardiovascular outcomes in diabetes: results from the REasons for Geographic and Racial Differences in Stroke (REGARDS) Study. *Diabetes Care*. 2016;39(1):101–109.