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LETTER

A Response to: Letter to the Editor with Regard to the Cost-Effectiveness of an Advanced Hybrid Closed-Loop System in People with Type 1 Diabetes: A Health Economic Analysis in Sweden

J. Jendle · M. I. Buompensiere · A. L. Holm · S. de Portu · S. J. P. Malkin · O. Cohen

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We would like to thank Levrat-Guillen and Ghazi for their interest in our recent analysis relating to the cost-effectiveness of advanced hybrid closed-loop (AHCL) insulin delivery relative to intermittently scanned continuous glucose monitoring (isCGM) in combination with multiple daily injections (MDI) or continuous subcutaneous insulin infusion (CSII) in people with type 1 diabetes (T1D) [1]. Levrat-Guillen and Ghazi have expressed concern over several aspects of the analysis. In an attempt to alleviate these concerns, the issues raised are addressed in a point-by-point fashion below.

In the absence of head-to-head comparisons of AHCL versus isCGM, Levrat-Guillen and Ghazi expressed concern over the clinical input data used to inform the analysis. For the isCGM arm, the HbA1c treatment effect was sourced from the real-world FUTURE study published by Charleer et al. [2]. Whilst several other potential data sources were available, the FUTURE study was chosen owing to the robust nature and design of the study (e.g., the study was conducted in specialist diabetes centers, with a large number of patients and long duration of follow-up) and a baseline HbA1c value that closely matched the levels observed in the study published by Collyns et al. [3], which was used to inform the AHCL arm. Levrat-Guillen and Ghazi mentioned three sources specifically (Gilbert et al. [4], Evans et al. [5], and Rose et al. [6]) but these studies were not considered for several reasons. The study published by Gilbert et al. [4] was considered inappropriate as the authors assessed the effectiveness of real-time CGM (rtCGM) rather than isCGM; utilization of this study would therefore require the assumption that isCGM and rtCGM are equivalent and evidence from a recent head-to-head study has suggested that this is not the case [7]. The meta-analysis by Evans et al. [5] reported a mean HbA1c reduction of 0.56% with isCGM; however, this was based on a large number of studies with baseline HbA1c values ranging from 6.79% to 10.28%. Finally, in the German observational study by Rose et al. [6], patients had a mean

J. Jendle (✉)
Institute of Medical Sciences, Örebro University, Campus USÖ, 701 82 Örebro, Sweden
e-mail: johan.jendle@oru.se

M. I. Buompensiere · S. de Portu · O. Cohen
Medtronic International Trading Sàrl, Tolechenaz, Switzerland

A. L. Holm
Medtronic Denmark, Copenhagen, Denmark

S. J. P. Malkin
Ossian Health Economics and Communications, Basel, Switzerland

baseline HbA1c of 8.15%, which was higher than that in the AHCL arm.

Levrat-Guillen and Ghazi also highlighted several limitations with regard to the clinical input data used for the AHCL arm, including the short study duration and that HbA1c calculations were based on sensor levels rather than laboratory measurements [3]. However, the 4-week duration of the study was in part mitigated by the crossover design, with each 4-week study period preceded by a 2–4-week run-in period and separated by a 2-week washout period. Moreover, the subsequent extrapolation of the short-term clinical data was acknowledged as a limitation in the "Discussion" section of the manuscript, and extrapolation of treatment effects is necessary in any long-term cost-effectiveness analysis. It should also be noted that the treatment effect sourced from the study by Collyns et al. [3] is of a similar magnitude to HbA1c reductions observed in studies using the earlier generation MiniMed 670G device [8–11]. For example, in a 3-month study of the MiniMed 670G system, mean HbA1c decreased from 7.4% to 6.9% in patients with previous CGM use and from 7.5% to 6.8% in patients with no prior CGM use [8]. Additionally, the authors of a recent real-world study on the MiniMed 780G system noted that, in routine clinical practice, the MiniMed 780G system was associated with superior outcomes relative to the MiniMed 670G system [12], suggesting that the 0.5% reduction modeled in the analysis may potentially represent a conservative scenario. The same MiniMed 670G studies also demonstrated a persistence of treatment effect over periods of up to 6 months. Given the evidence for the MiniMed 670G system, as well as the added sophistication of the MiniMed 780G system, it was deemed reasonable to assume a similar persistence of treatment effect with AHCL. The lack of head-to-head trials comparing isCGM with AHCL was also acknowledged in the manuscript. Further, this comparison is the subject of ongoing research [13] and, as Levrat-Guillen and Ghazi suggest, it would be prudent to repeat this analysis once head-to-head data become available.

In the cost-effectiveness analysis, it was assumed that the use of AHCL would reduce the incidence of severe hypoglycemic events to zero. Levrat-Guillen and Ghazi suggested that the evidence base for this assumption is lacking. However, Carlson et al. [14] reported no severe hypoglycemic events with AHCL over a 90-day study period, and data from studies on earlier generation devices, including the MiniMed 670G system, are in line with the assumptions applied in the analysis (e.g., Cordero et al. [8] and Petrovski et al. [15]).

A further concern raised by Levrat-Guillen and Ghazi pertained to assumptions around the utility benefit assumed to be conferred to simulated patients in the AHCL arm owing to a reduction in fear of hypoglycemia (FoH). As noted by Levrat-Guillen and Ghazi, this assumption was based on the findings of the 2013 INTERPRET study by Nørgaard et al. [16]. Whilst this study examined the effectiveness of sensor-augmented pump therapy (SAP) rather than AHCL, it was considered reasonable to assume that, given the additional sophistication of AHCL relative to SAP, this benefit would also apply to AHCL.

No utility benefit relating to reduced FoH was applied to the isCGM arm. While Levrat-Guillen and Ghazi drew attention to the fact that a reduction in FoH was reported by Al Hayek et al. [17] in a study conducted in children with T1D in Saudi Arabia, the data presented were collected using the child rather than the adult version of the Hypoglycemia Fear Survey (HFS) and may therefore be of limited generalizability to adults with long-standing disease. Moreover, in the FUTURE study, which was used to inform the isCGM arm, no significant change in HFS worry score was reported [2]. Similarly, recent data from a 6-month prospective randomized controlled trial that directly compared rtCGM with isCGM reported that FoH (measured using the HFS worry subscale) decreased from 18.8 to 15.4 with rtCGM, but only from 18.7 to 18.0 with isCGM, resulting in a significant between-group difference in favor of rtCGM at 6 months [7]. A point worthy of note with regard to FoH is that isCGM requires engagement from the user, whereas rtCGM devices with alert features will alert the user to hypoglycemia (or predicted imminent hypoglycemia) without engagement from the

Table 1 Findings of additional sensitivity analyses

Analysis	Quality-adjusted life expectancy, QALYs			Total lifetime costs, SEK			ICER, SEK per QALY gained
	AHCL	isCGM plus MDI or CSII	Difference	AHCL	isCGM plus MDI or CSII	Difference	
Cost of SHE + 20%	14.25	12.31	1.95	3,414,589	2,698,751	715,838	367,756
Cost of SHE − 20%	14.25	12.31	1.95	3,414,589	2,675,612	738,977	379,644
QoL benefit with reduced FoH − 50%	13.71	12.31	1.40	3,414,589	2,687,181	727,408	518,060
[a]SHE rate reduced by 50%	14.25	12.66	1.60	3,414,589	2,620,182	794,407	497,967

AHCL advanced hybrid closed-loop, *CSII* continuous subcutaneous insulin infusion, *ICER* incremental cost-effectiveness ratio, *isCGM* intermittently scanned continuous glucose monitoring, *MDI* multiple daily injections, *QALY* quality-adjusted life year, *SHE* severe hypoglycemic event

[a]Refers to a 50% reduction in the incidence of SHEs in the isCGM arm

user. AHCL goes further by both detecting hypoglycemia and adjusting insulin delivery accordingly. Consequently, it is reasonable to assume that AHCL would confer a greater utility benefit relative to isCGM in terms of reduced FoH, particularly in specific instances such as in patients with an impaired awareness of hypoglycemia, which can be a key risk factor for FoH [18].

Finally, to mitigate the concerns around a lack of sensitivity analyses, a series of additional sensitivity analyses have been performed around the incidence rates and costs of severe hypoglycemic events, as well as the utility benefit associated with reduced FoH (Table 1). As shown in Table 1, and acknowledged in the "Discussion" section of the manuscript, reduced FoH is a key driver of cost-effectiveness.

Declarations

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REFERENCES

1. Levrat-Guillen F, Ghazi T. Cost-effectiveness of intermittently scanned continuous glucose monitoring versus advanced hybrid closed-loop systems in type 1 diabetes: comment on Jendle et al. Diabetes Ther. https://doi.org/10.1007/s13300-022-01251-x.

2. Charleer S, De Block C, Van Huffel L, et al. Quality of life and glucose control after 1 year of nationwide reimbursement of intermittently scanned continuous glucose monitoring in adults living with type 1 diabetes (FUTURE): a prospective observational real-world cohort study. Diabetes Care. 2020;43:389–97.

3. Collyns OJ, Meier RA, Betts ZL, et al. Improved glycemic outcomes with medtronic minimed advanced hybrid closed-loop delivery: results from a randomized crossover trial comparing automated insulin delivery with predictive low glucose suspend in people with type 1 diabetes. Diabetes Care. 2021;44:969–75.

4. Gilbert TR, Noar A, Blalock O, Polonsky WH. Change in hemoglobin A1c and quality of life with real-time continuous glucose monitoring use by people with insulin-treated diabetes in the landmark study. Diabetes Technol Ther. 2021;23:S35–9.

5. Evans M, Welsh Z, Ells S, Seibold A. The Impact of flash glucose monitoring on glycaemic control as measured by HbA1c: a meta-analysis of clinical trials and real-world observational studies. Diabetes Ther. 2020;11:83–95.

6. Rose L, Klausmann G, Seibold A. Improving HbA1c control in type 1 or type 2 diabetes using flash glucose monitoring: a retrospective observational analysis in two German centres. Diabetes Ther. 2021;12:363–72.

7. Visser MM, Charleer S, Fieuws S, et al. Comparing real-time and intermittently scanned continuous glucose monitoring in adults with type 1 diabetes (ALERTT1): a 6-month, prospective, multicentre, randomised controlled trial. Lancet. 2021;397(10291):2275–83.

8. Cordero TL, Garg SK, Brazg R, et al. The effect of prior continuous glucose monitoring use on glycemic outcomes in the pivotal trial of the MiniMed™ 670G hybrid closed-loop system. Diabetes Technol Ther. 2017;19:749–52.

9. McAuley SA, Lee MH, Paldus B, et al. Six months of hybrid closed-loop versus manual insulin delivery with fingerprick blood glucose monitoring in adults with type 1 diabetes: a randomized controlled trial. Diabetes Care. 2020;43:3024–33.

10. Lepore G, Scaranna C, Corsi A, Dodesini AR, Trevisan R. Switching from suspend-before-low insulin pump technology to a hybrid closed-loop system improves glucose control and reduces glucose variability: a retrospective observational case-control study. Diabetes Technol Ther. 2020;22(4):321–5.

11. Garg SK, Weinzimer SA, Tamborlane WV, et al. Glucose outcomes with the in-home use of a hybrid closed-loop insulin delivery system in adolescents and adults with type 1 diabetes. Diabetes Technol Ther. 2017;19:155–63.

12. Da Silva J, Lepore G, Battelino T, et al. Real-world performance of the MiniMed™ 780G system: first report of outcomes from 4120 users. Diabetes Technol Ther. 2021. https://doi.org/10.1089/dia.2021.0203.

13. ClinicalTrials.gov. Advanced hybrid closed loop study in adult population with type 1 diabetes (ADAPT). https://clinicaltrials.gov/ct2/show/NCT04235504. Accessed Jan 24, 2022.

14. Carlson AL, Sherr JL, Shulman DI, et al. Safety and glycemic outcomes during the MiniMed™ advanced hybrid closed-loop system pivotal trial in adolescents and adults with type 1 diabetes. Diabetes Technol Ther. 2021. https://doi.org/10.1089/dia.2021.0319.

15. Petrovski G, Al Khalaf F, Campbell J, et al. One-year experience of hybrid closed-loop system in children and adolescents with type 1 diabetes previously treated with multiple daily injections: drivers to successful outcomes. Acta Diabetol. 2021;58(2):207–13.

16. Nørgaard K, Scaramuzza A, Bratina N, et al. Routine sensor-augmented pump therapy in type 1 diabetes: the INTERPRET study. Diabetes Technol Ther. 2013;15:273–80.

17. Al Hayek AA, Robert AA, Al Dawish MA. Evaluation of FreeStyle Libre flash glucose monitoring system on glycemic control, health-related quality of life, and fear of hypoglycemia in patients with type 1 diabetes. Clin Med Insights Endocrinol Diabetes. 2017;10(10):1179551417746957.

18. Anderbro T, Amsberg S, Adamson U, et al. Fear of hypoglycaemia in adults with type 1 diabetes. Diabet Med. 2010;27(10):1151–8.