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Reply to Letter by Alexander Seibold on “Impact of Switching from Intermittently Scanned to Real-Time Continuous Glucose Monitoring Systems in a Type 1 Diabetes Patient French Cohort: An Observational Study of Clinical Practices” by Yannis Préau, et al. (doi: 10.1089/dia.2020.0674)

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Dear Editor,

WE THANK ALEXANDER SEIBOLD for his comments¹ on our observational study evaluating, retrospectively and in a real-world setting, the benefits in glucose management of a switch from an intermittently scanned continuous glucose monitoring (isCGM) to a real time CGM (rtCGM) systems in type 1 diabetes (T1D) patients with persistent glycemic disorders (hypoglycemia issue and/or high level of hemoglobin A1c [HbA1c]) despite an intensified insulin regimen and use of a FreeStyle Libre 1 (FSL1) device for at least 1 year.²

First, our monocentric study was not designed as a study comparing the efficiency of two different devices and was not funded by any company; it is an observational study of clinical practice. Thus, the notion of superiority of one device to another is never mentioned, as the design and the context of the study did not aim supporting this. As explained in our article, in our department of diabetology, we propose, as one “therapeutical option,” a switch to rtCGM (Dexcom G4 platinum [DG4] because it is a system reimbursed by the French Health Insurance) when patients with poor glycemic control on FSL1 want to keep their usual insulin pump (for continuous subcutaneous insulin infusion) or to continue using multiple daily insulin injection. Only a moderate fraction of our followed up T1D population is concerned, explaining the limited number of patients whose data are reportable. In addition, out of 25 concerned medical folders, 7 were not usable to respect the availability of the needed data (i.e., due to missing data when DG4 use was stopped) or the adherence to the Therapeutic Patient Educational Program (rejected when missing planned visits) that is essential in our clinical practice on CGM. The withdrawal of such folders did

not constitute a study bias for us but rather a logical way to do. As already mentioned in our article, we agree that the small number of patients is a limitation, and those results have to be considered with caution and in the narrow conditions of the specific profile of our observed patients, that is, patients encountering difficulties in making optimal use of the FSL system in everyday life for different reasons (decline in adherence, lack of educational reminders on the behaviors to adopt according to displayed values and trends arrows, and repeated skin reactions to the sensor)^{3,4} explaining the moderate number of daily scans (average of 6 scans/day), whereas an almost linear relationship exists between scans frequency and the improvement of CGM metrics (even beyond 14 scans/day).^{5,6} Also, even though averages are needed in scientific publications, we think that considering the benefits for each patient individually is more pertinent to a physician’s point of view rather than considering a global impact on a group of population, which cannot be generalizable, especially when patients can be responders or nonresponders. In the light of this opinion, it was satisfactory that 50% of the followed up patients underwent improvement from switching FSL1 to DG4 for a 6-month period in our study. The reasons why only half of the studied patients underwent benefits deserve further interest.

Second, as mentioned in our article as a limitation,² we agree that all sensor systems exhibit different accuracy (in euglycemic and even more in hypoglycemic range), sensitivity, and specificity in functioning (e.g., glycemia calibration, presence of alarms or not, need of scanning or not, implantation site, bleeding on insertion site, and sensor lifetime)⁷ in line with the commentary on the data reported by A. Seibold¹ as well as by M. Reddy and colleagues in a response to a

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previous letter for the I HART CGM study.⁸ Such points are of high importance in the efficiency of sensors to inform on the achievability of ambulatory glucose profile targets as defined by the Advanced Technologies and Treatments for Diabetes (ATTD) consensus for a good glycemia management.⁹ Indeed, as raised by A. Seibold¹ the hypoglycemia level is underestimation by +19% for DG4 and by +4.9% for FSL1 when reading interstitial glucose in the range 61–80 mg/dL. If transposing this limitation by applying such respective “correcting factor” to our previous data for time below range <70 mg/dL, it emerges a still significant difference on its decrease with a mean (standard deviation [SD]) change of −5.03 (6.13) percentage points ($P=0.0029$) at 3 months of DG4 use, and a mean (SD) change of −4.13 (6.66) percentage points ($P=0.0176$) at 6 months of DG4 use. We do not mean this corrective simulation has to be done, but if done the results are still optimistic. Nevertheless, whatever the device used, we have noticed in our article that few of these patients at high risk of hypoglycemia or/and high level of HbA1c were reaching the targets defined by the ATTD.

Third, the relationship between changes in biological HbA1c and average glucose or with the glucose management indicator (GMI) or with improvement in time in range (TIR) 70–180 mg/dL is not so clear. Indeed, in the I HART CGM study extension phase investigating a switch from FSL1 to Dexcom G5, a significant change in TIR was not accompanied by changes in HbA1c in the T1D patients studied that exhibited all a baseline level <8%.¹⁰ In our study,² in a statistical point of view, HbA1c and GMI mean values with FSL1 or with DG4 (at 3 or 6 months of use) were not significantly different ($P>0.5$ or $P>0.14$, respectively), so there was no trend to consider. However, HbA1c levels were more heterogeneous in our study,² with 50% of patients ($n=9$) having an elevated HbA1c ($\geq 8\%$) at baseline (i.e., at the stop of FSL1), and 6 out of 9 underwent, at 3 or 6 months of DG4 use, respectively, a decrease in HbA1c (-0.67 ± 0.33 or -0.43 ± 0.46 percentage points), in GMI (-0.44 ± 1.33 or -0.53 ± 1.13 percentage points), in time above range >180 mg/dL (-3.3 ± 16.7 or -10.2 ± 15.7 percentage points), in average glucose (-11.2 ± 41.7 mg/dL or -21.7 ± 28.9 mg/dL), and an increase in TIR ($+10.4 \pm 8.4$ or $+11.9 \pm 10.9$ percentage points). These data, obtained for patients with elevated HbA1c, are in agreement with the article of Beck et al. showing an increase of 10 percentage points in TIR being predictive of a reduction of HbA1c of −0.6 points on average in 545 T1D patients.¹¹ The nondecrease in HbA1c for the other patients despite an increase in TIR could be due to red blood cell lifespan or other factors influencing HbA1c levels unrelated to the degree of glycemia (chronic renal disease, hemoglobinopathies or hemoglobin variants, hypertriglyceridemia, and hyperbilirubinemia),¹² and was observed by Beck et al. since a 10 percentage points of increase in TIR can correspond to a wide variation in HbA1c (from −1.74 to +0.60 points).

Finally, our study showed benefits on glucose management in a specific group of T1D patients (high risk of hypoglycemia and/or elevated HbA1c) after switching from FSL1 (not optimally used) to DG4 during 3 months of use, benefits that plateaued at 6 months (metrics values not significantly different), and it will be of high interest to observe the evolution on a longer period of follow-up that is, at 12 months (ongoing analyses). We believe in the absolute need for data implying the switch from different combinations of systems (isCGM to

isCGM, rtCGM to isCGM, rtCGM to rtCGM, and isCGM to rtCGM) over long monitoring periods and concerning large number of patients, whereas considering analytical limits in the comparison of CGM data from different devices but having to be part of a search for overall glycemic benefit (including biological HbA1c) and also quality of life and satisfaction for each patient. The principal goal is the setting of personalized medicine counseling the glucose monitoring device best suited to each patient.

Author Disclosure Statement and Funding Information

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