Fully Integrated Artificial Pancreas in Type 1 Diabetes

Modular Closed-Loop Glucose Control Maintains Near Normoglycemia

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Integrated closed-loop control (CLC), combining continuous glucose monitoring (CGM) with insulin pump (continuous subcutaneous insulin infusion [CSII]), known as artificial pancreas, can help optimize glycemic control in diabetes. We present a fundamental modular concept for CLC design, illustrated by clinical studies involving 11 adolescents and 27 adults at the Universities of Virginia, Padova, and Montpellier. We tested two modular CLC constructs: standard control to range (sCTR), designed to augment pump plus CGM by preventing extreme glucose excursions; and enhanced control to range (eCTR), designed to truly optimize control within near normoglycemia of 3.9–10 mmol/L. The CLC system was fully integrated using automated data transfer CGM→algorithm→CSII. All studies used randomized crossover design comparing CSII versus CLC during identical 22-h hospitalizations including meals, overnight rest, and 30-min exercise. sCTR increased significantly the time in near normoglycemia from 61 to 74%, simultaneously reducing hypoglycemia 2.7-fold. eCTR improved mean blood glucose from 7.73 to 6.68 mmol/L without increasing hypoglycemia, achieved 97% in near normoglycemia and 77% in tight glycemic control, and reduced variability overnight. In conclusion, sCTR and eCTR represent sequential steps toward automated CLC, preventing extremes (sCTR) and further optimizing control (eCTR). This approach inspires compelling new concepts: modular assembly, sequential deployment, testing, and clinical acceptance of custom-built CLC systems tailored to individual patient needs.

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The maintenance of close-to-normal blood glucose (BG) levels slows the onset and progression of long-term microvascular complications in patients with type 1 diabetes (1); therefore, the ultimate therapeutic goal of type 1 diabetes is to restore near normoglycemia (2). In the past decade, the advent of both continuous glucose monitoring (CGM) (3–5) and automated CGM-assisted insulin delivery, known as artificial pancreas or closed-loop control (CLC) (6,7), have accelerated the achievement of this goal. Although the traditional therapeutic strategies target long-term average BG reduction measured by HbA_{1c} (1,8), CLC aims to minimize, in real time, glucose variability and prevent extreme glucose excursions (e.g., hypo- and hyperglycemia) (9). This objective is achieved via frequent insulin adjustment modulated by a CLC algorithm, which takes into account CGM readings and the effects of previous insulin infusions to continuously compute the amount of insulin dose to be administered (10).

Historically (see Cobelli et al. for a review) (7), systems controlling BG automatically can be traced back decades ago to when the possibility for external BG regulation was demonstrated using intravenous BG measurements and intravenous infusions of insulin and glucose (11,12). However, these systems were cumbersome and unsuitable for long-term, or outpatient, use. The development of both CGM and portable devices for continuous subcutaneous insulin infusion (CSII) incited the implementation of subcutaneous CLC systems (13). Promising results have been reported by several research groups (7,13–22). Most of these studies point out the superiority of CLC over standard CSII therapy in terms of increased time within target glucose range (typically 3.9–10 mmol/L), reduced incidence of hypoglycemia, and better overnight control.

However, to date, there are no randomized crossover studies of fully integrated CLC, defined as having all of the following three components: *1*) automated data transfer from the CGM to the controller, *2*) real-time control action, and *3*) automated command of the insulin pump. Only one previously reported study has a state-of-the-art randomized crossover design (18), but it lacks automated data transfer (15). Conversely, the studies that use fully integrated glucose control (13,14,17,19–22) do not follow a randomized crossover design.

We have developed a novel approach to CLC algorithm design based on a modular architecture concept (7,23,24).

Such a modular architecture would allow diverse components to be seamlessly integrated in a functional hierarchical system that can be sequentially deployed in clinical and ambulatory studies. Modularity allows a stepwise regulated approach: first, algorithmic modules designed to improve patient safety are implemented; and second, increasingly complex modules designed to optimally modulate insulin delivery in real time are used.

With this background in mind, we now present two multicenter randomized crossover trials using two fully integrated subcutaneous CLC systems based on the modular architecture concept (Fig. 2). Both systems aimed at maintaining near normoglycemia in the 3.9–10 mmol/L target range and implemented a strategy known as control to range (CTR). The first system, standard CTR (sCTR), included a safety supervision module (SSM) mitigating the risk for hypoglycemia, and an sCTR algorithm activated when hyperglycemia was predicted. The task of sCTR was to prevent hypoglycemia and mitigate extreme hyperglycemia, without truly aiming for optimal glucose control. The second system, enhanced CTR (eCTR), included the same SSM to prevent hypoglycemia but coupled with a more sophisticated model predictive control (MPC) algorithm. The task of eCTR was optimal glucose control within a target range.

For both algorithms, we assess effectiveness of the system as reflected by time spent in near normoglycemia (3.9–10 mmol/L), average glucose, and glucose variability. In addition, we include algorithm-specific metrics corresponding to the design of the two algorithms: degree of mitigation of hypoglycemia for sCTR and time spent in tight glycemic control (4.4–7.8 mmol/L) for eCTR.

RESEARCH DESIGN AND METHODS

A total of 38 subjects with type 1 diabetes, including 11 adolescents (aged 12–18 years) and 27 adults (aged 21–65 years), were enrolled in two randomized crossover studies at the University of Virginia General Clinical Research Center (UVA), Montpellier University Hospital and Clinical Investigation Center INSERM 1001 (MON), and at the Department of Internal Medicine, University of Padova (PAD).

Study 1 enrolled 11 adolescents and 9 adults at UVA (12 adolescents and 12 adults screened) and 6 adults at MON (6 screened). Study 2 recruited 12 adults: 6 at MON (6 screened) and 6 at PAD (6 screened). Summary demographics are presented in Table 1.

All enrolled patients finished the studies, but five datasets were excluded from the analysis as follows: *1*) in study 2, three datasets were excluded as a result of software malfunction and/or sensor failures and one additional dataset was partially excluded (the night portion has been removed from the overnight analysis because of extended postprandial effect in both control and treatment admission); and *2*) in study 1, for unexplained reasons, one adult patient had very different metabolic characteristics between admissions 1 and 2 (doubled insulin sensitivity), precluding the comparison between the two admissions.

Protocols. Studies 1 and 2 were approved by the ethical boards of the participating institutions and by relevant regulatory agencies and were registered under the following reference numbers: 14356 and 14758 (http://www.virginia.edu/vpr/irb/hsr/index.html), 2009-A00421–56 (www.afssaps.sante.fr), and 2039P (www.sanita.padova.it). At each site, after obtaining written informed consent, patients were randomized to determine the order of open-loop CSII and CLC. Patients were equipped with two CGM devices, either Dexcom 7 (Dexcom, Inc., San Diego, CA) or Navigator (Abbott Diabetes Care, Alameda, CA), at least 24 h before admission and after careful instruction on their use. CGM devices were calibrated as per manufacturer schedule, using self-monitoring of BG measurements before admission and YSI measurements during admission. Navigator was used at MON and Dexcom 7 was used at the other two sites; a posteriori analysis of CGM accuracy led to the conclusion that both CGMs performed similarly in terms of mean absolute difference and mean absolute relative difference (nonsignificant two-sample t test), and accuracy was improved compared with "at home" use, probably because of YSI calibrations. During the open-loop admission, patients used their own insulin pump to control BG according to capillary BG measured at patients' discretion and at least before and 2 h after meals and snacks, at bedtime, and before and after exercise. Just before the closed-loop admission, one sensor was chosen by the study physician based on accuracy and signal quality and was used thereafter to drive the CLC system; the second sensor remained as backup in case of a primary sensor failure. Patients were equipped with Omnipod Insulin Management Systems (Insulet Corporation, Bedford, MA) filled with Humalog insulin (Eli Lilly and Company, Indianapolis, IN).

Studies 1 and 2 used identical protocols, which lasted 22 h as depicted by the timeline in Fig. 1, including 30 min of moderate exercise (adults: 50% $V_{O_{2max}}$; adolescents: OMNI rate of perceived exertion <3) (25), a patient-selected meal (1.08 ± 0.24 g carbohydrate per kg of weight, identical for both admissions),

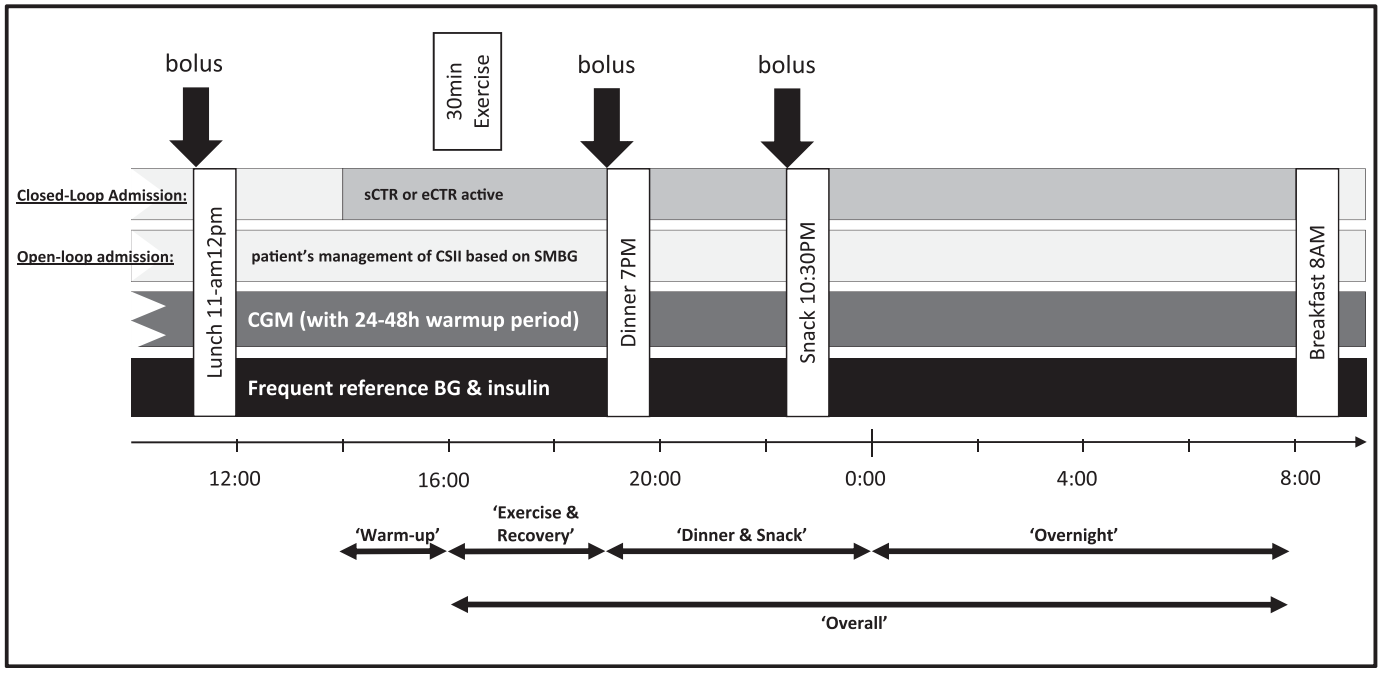

FIG. 1. Design and profile of randomized clinical trials and timeline of inpatient admissions.

TABLE 1
Demographic characteristics of studied patients at all three clinical centers

	Patient, *n* (%)	Mean (SD)
Adult population for study 1 (N = 15)		
Average age (years)		41 (10)
Male participants	9 (64)	
Average HbA_{1c} (%)		7.3 (0.9)
Average BMI		24.5 (3.0)
Average daily insulin use (units/kg)		0.54 (0.15)
Average time since diagnosis (years)		25.3 (9.1)
Average time on pump (years)		11 (11)
Adult population for study 2 (N = 12)		
Average age (years)		38 (10)
Male participants	8 (67)	
Average HbA_{1c} (%)		7.5 (0.9)
Average BMI		23.4 (2.1)
Average daily insulin use (units/kg)		0.50 (0.10)
Average time since diagnosis (years)		21.7 (8.7)
Average time on pump (years)		3.1 (2.4)
Adolescent population for study 1 (N = 11)		
Average age (years)		14.5 (1.5)
Male participants	6 (55)	
Average HbA_{1c} (%)		8.6 (0.8)
Average BMI percentile (more meaningful for teens)		63.8 (19.2)
Average daily insulin use (units/kg)		0.9 (0.2)
Average time since diagnosis (years)		6.2 (3.8)
Average time on pump (years)		4.4 (3.1)

a standardized snack (20 g carbohydrate), and an 18-h CLC on the experimental days. Reference glucose values were obtained using plasma measurements (YSI 2300/2700, Yellow Spring Instruments) at least every hour over the span of the protocol (every 30 min at UVA) and more frequently during and for 1 h after exercise (every 5 and 10 min, respectively) and for an hour after meals (every 10 min). Hypoglycemia was defined as YSI reading <3.9 mmol/L or the occurrence of hypoglycemic symptoms (sweating, trembling, difficulty in thinking, dizziness, or impaired coordination). Hypoglycemia was treated with glucose tablets, the amount of which was left to physician discretion.

Control algorithms. The control algorithms used by studies 1 and 2—sCTR and eCTR, respectively—were designed and tested in silico using computer simulation (26), and each algorithm had a different focus: in study 1, the emphasis was on safety and prevention of hypo- and hyperglycemia, while in study 2, the emphasis was on tight glycemic control. Nevertheless, as outlined above, both control algorithms relied on the same modular architecture and belonged to the same CTR class (23).

Modular architecture. The modular architecture of the CTR system comprises *1*) the bottom system layer (SSM), which operates continuously and is in charge of prevention of hypoglycemia—the major barrier to tight glycemic control (27); *2*) the middle layer (range control module), which is responsible for real-time correction of insulin dosing and is different in sCTR and eCTR; and *3*) the top layer, which tunes the real-time control layer using clinical parameters and historical data, which was done off-line in this implementation. The communications between the CGM sensor, the CTR system, and the insulin pump were handled by the artificial pancreas system (APS) software (28).

The two algorithms presented below include the SSM (bottom layer) and different range controllers (middle layer).

sCTR: Study 1. The two modules of sCTR are the SSM and a standard range control module that avoids prolonged hyperglycemic excursions. Both modules use a real-time estimate of the patient's metabolic state based on CGM and insulin infusion data. This estimate is used for prediction of the risks of hypo- and hyperglycemia 30–45 min ahead of the event. If a risk for hypoglycemia is predicted, the SSM attenuates automatically any insulin requests proportionally to the predicted risk level. How aggressively the system attenuates insulin is determined with readily available patient characteristics (e.g., body weight, insulin-to-carbohydrate ratio, and basal insulin delivery) (24). If a risk for hyperglycemia is predicted, the range controller introduces a correction bolus using the predicted plasma glucose and the patient's CSII parameters to reach a predetermined glucose target (8.3 mmol/L); the system injects only half of the computed bolus and can do so once every hour. Premeal boluses are calculated by the patients, based on their usual routine. The meal carbohydrate content was provided to the patient as measured in the clinical research center (CRC) kitchen.

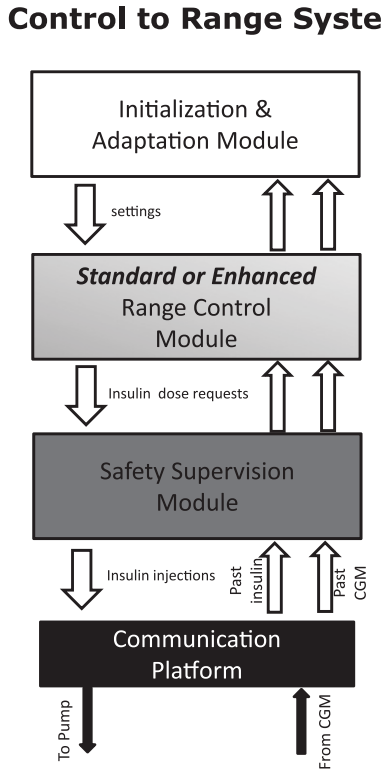

FIG. 2. Modular architecture of CTR.

eCTR: Study 2. The two modules of the eCTR are the SSM and an enhanced range control module based on an MPC algorithm that aims to maintain glycemia in a target range. eCTR also uses insulin-on-board constraints (29) intended to prevent insulin overdose during intensified therapy.

The rationale behind MPC was presented in detail in a recent review (7). Controller aggressiveness was individualized for each subject based on readily available patient characteristics (e.g., body weight, insulin-to-carbohydrate ratio, and basal insulin delivery) (30). In this application, the MPC worked using information from the individual's conventional therapy. Premeal boluses were triggered by the patient, with the carbohydrate amount measured in the CRC kitchen but automatically calculated by eCTR.

Technical details for the sCTR and eCTR algorithms can be found in a previous publication (30) where they are tested and compared in silico.

Performance indices. Algorithm performance has been assessed by calculating several indices derived from the measured BG profiles: the percent time spent in near normoglycemia (3.9–10 mmol/L), the percent time in tight glycemic range (4.4–7.8 mmol/L), mean glucose, intrasubject glucose variability (calculated as SD), and the number of hypoglycemic events per subject. In addition, the Low Blood Glucose Index (LBGI) and High Blood Glucose Index (HBGI), together with the BG Risk Index, were used as metrics of risk for hypo- and hyperglycemia and overall glucose variability (9). For detailed analysis, the full admission was segmented into four time windows: controller warm-up (2 P.M. to 4 P.M.), exercise and recovery (4 P.M. to 7 P.M.), dinner and snack (7 P.M. to midnight), and overnight (midnight to 8 A.M., no large disturbances). The warm-up period was excluded from the overall analysis.

Statistical analysis. Comparison between open- and closed-loop admissions was performed using paired t tests and ANOVA with covariates when necessary; all results are provided as mean ± SE of the mean, open-loop versus closed-loop admission, unless specified otherwise.

RESULTS

Study 1: sCTR versus open-loop CSII. Time spent in near normoglycemia increased significantly overall from 61.5 ± 5.2% (open-loop session) to 74.4 ± 3.9% (sCTR)

(P = 0.01), with a maximal effect overnight (53.9 ± 7.8 vs. 74.1 ± 6.8%, P = 0.016). As would be expected by the design of sCTR, time spent in tight glycemic range (4.4–7.8 mmol/L) did not differ between the two admissions overall (34.9 ± 5.0 vs. 37.4 ± 5.4%, P = 0.66) or overnight (30.8 ± 0.7 vs. 32.7 ± 0.7%, P = 0.80) see Fig. 3.

Improved glycemic control was achieved with simultaneous 2.7-fold reduction in hypoglycemia from a total of 27 hypoglycemic events during open loop to 10 events during sCTR, a reduction that corresponds to 1.08 ± 0.27 versus 0.4 ± 0.13 events/patient (P = 0.01) and to a significant reduction in the risk for hypoglycemia as indicated by the LBGI (1.51 ± 0.31 vs. 0.72 ± 0.18, $P < 0.01$). A particularly prominent sixfold reduction in hypoglycemia was observed overnight. Hypoglycemic events were most likely during exercise or within 3 h after dinner and almost never occurred on CLC during recovery (0.04 events/patient) and overnight (0.08 events/patient). Because the study protocol mandated treatment of hypoglycemia once it had occurred, the extent of the hypoglycemic events could not be assessed. Amount of treatment per hypoglycemic event was recorded and showed no difference between admission (each hypoglycemia event was treated with, respectively, 14.94 vs. 12.33 g carbohydrate, P = 0.58 independent sample t test).

Average glucose was not significantly reduced overall (8.82 ± 0.54 vs. 8.34 ± 0.28 mmol/L, P = 0.36) or overnight (9.44 ± 0.72 vs. 8.47 ± 0.39 mmol/L, P = 0.09), whereas a significant decrease in the overnight risk for hyperglycemia was observed, as indicated by the HBGI (9) (8.39 ± 1.85 to 4.35 ± 0.82, P = 0.014). Average glucose profiles ± and 25–75% quantiles for open-loop CSII versus sCTR are presented in Fig. 5 (upper panel).

Glucose variability, as measured by the BG Risk Index (9), was significantly reduced from 8.19 ± 1.19 to 5.05 ± 0.47 (P = 0.01), with maximum effect overnight (9.62 ± 1.66 vs. 4.9 ± 0.74, $P < 0.01$). Intrasubject variability (indicated by SD of BG, mmol/L) was significantly reduced overall (2.46 ± 0.21 vs. 1.87 ± 1.5, P = 0.02) and overnight (1.60 ± 0.22 vs. 1.05 ± 0.10, P = 0.02) (Traces are presented in Supplementary Fig. 1).

Study 2: eCTR versus open-loop CSII. We observed a significant decrease in the overall average plasma glucose (mmol/L) from 7.74 ± 0.44 (open-loop session) to 6.68 ± 0.28 (eCTR) ($P < 0.01$), with maximum effect reached overnight (7.71 ± 0.70 to 6.12 ± 0.38, P = 0.042). The decrease in the risk for hyperglycemia as indicated by the HBGI was marginal overall (3.63 ± 0.87 vs. 2.07 ± 0.74, P = 0.07) and during dinner and snack (3.83 ± 1.41 vs. 2.62 ± 0.62, P = 0.23) but significant overnight (3.67 ± 1.22 vs. 0.79 ± 0.34, P = 0.02).

The overall percent time in near normoglycemia increased significantly from 76.8 ± 5.0 to 90.1 ± 3.4% (P = 0.05), with maximal eCTR performance of 97.6 ± 2% achieved overnight (Fig. 4). Percent time in tight control (4.4–7.78 mmol/L)

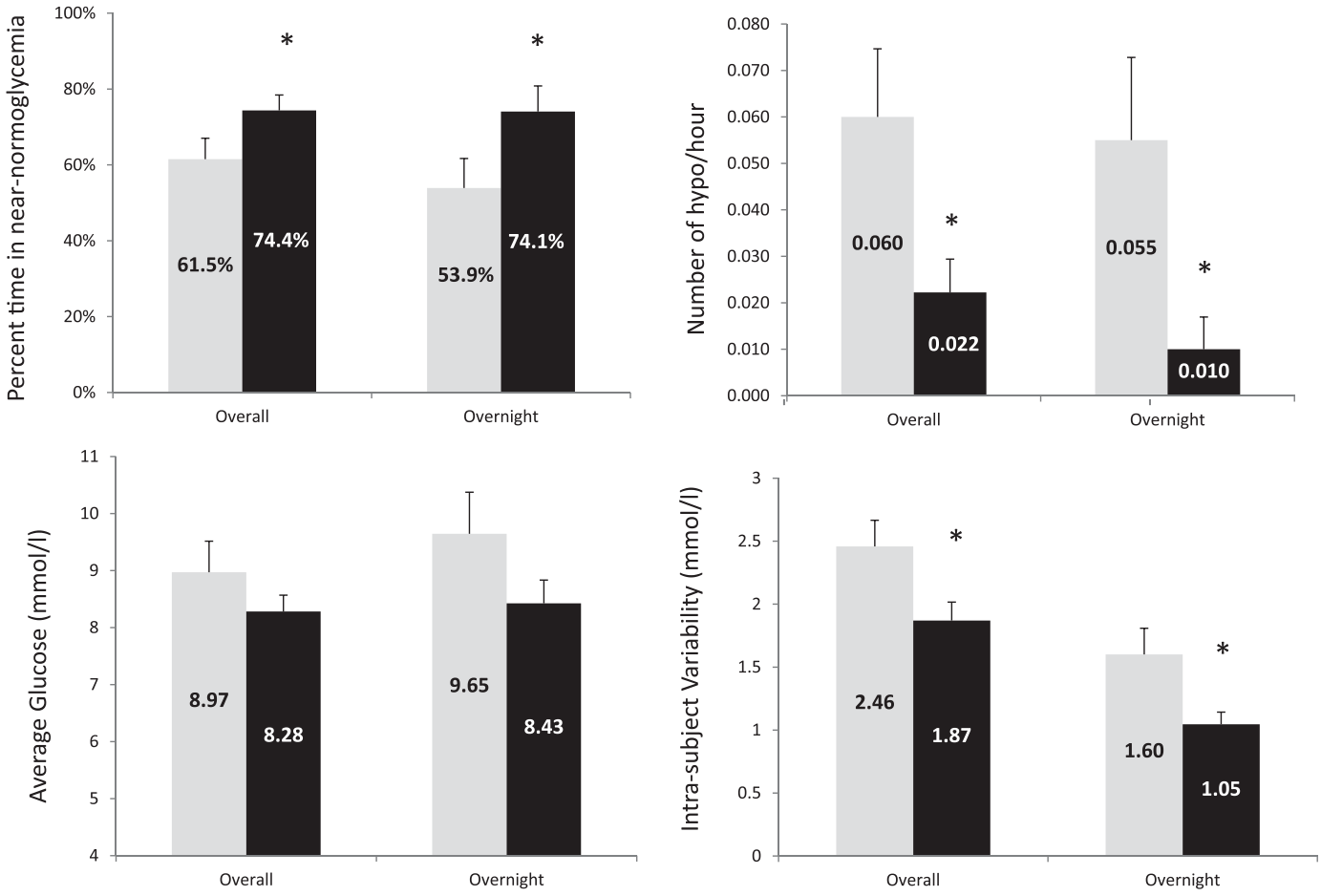

FIG. 3. Primary outcomes of sCTR: Time in near normoglycemia (3.9–10 mmol/L), average glucose, intrasubject variability, and occurrence of hypoglycemia (hypo) during open- and closed-loop admissions, contrasted by overall and overnight periods. *$P < 0.05$. Open-loop CSII, gray bar; sCTR, black bar.

increased (but not significantly) overall from 47.2 ± 6.6 to 62.0 ± 5.2% (P = 0.09) and significantly overnight from 42.7 ± 11.2 to 79.3 ± 8.1% (P = 0.04). Glucose control was achieved without apparent increase in the risk of hypoglycemia (1.4 vs. 1.6 events/patient in open loop vs. eCTR, P = 0.43) as confirmed by the LBGI (overall: 0.62 ± 0.19 vs. 1.05 ± 0.23, P = 0.09; overnight: 0.88 ± 0.41 vs. 1.08 ± 0.58, P = 0.43). Hypoglycemic events were most likely during and after exercise and between dinner and snack (1.1 events/patient) but were less frequent overnight (0.4 events/patient).

Finally, using the BG Risk Index, we confirmed the improvement shown in percent time in target range: the index was significantly reduced overnight (4.37 ± 0.88 vs. 2.37 ± 0.67, P = 0.04) and marginally reduced overall (4.68 ± 0.76 vs. 3.26 ± 0.69, P = 0.41) and during dinner and snack (4.88 ± 1.24 vs. 3.84 ± 0.84, P = 0.25). Intrasubject variability (mmol/L) was marginally reduced overall (2.13 ± 0.21 vs. 1.81 ± 0.21, P = 0.27) but significantly reduced overnight (1.35 ± 0.14 vs. 0.84 ± 0.16, P = 0.045).

Average glucose profiles and 25–75% quantiles for open-loop CSII versus eCTR and sCTR are presented in Fig. 5 (Traces are presented in Supplementary Fig. 2).

Additional comparisons

sCTR versus eCTR. Although direct comparison between sCTR and eCTR is not justified on all performance parameters because of their essential design differences, we can draw some conclusions comparing similar features and selecting similar populations (adult only). We used univariate ANOVA with CSII performance included as a covariate to compensate for interindividual differences for all continuous variables, except for hypoglycemia counts, which necessitated a nonparametric Mann-Whitney U test. This analysis led to the following conclusions: *1*) eCTR and sCTR both increased time spent in near normoglycemia similarly (P = 0.21); *2*) eCTR increased overnight time spent in tight glycemic control further, compared with sCTR (P = 0.036); *3*) eCTR decreased mean BG further than sCTR overall (P = 0.012), but overnight comparison was not conclusive (P = 0.06); *4*) eCTR and sCTR both decreased glycemic variability similarly (P = 0.46); and *5*) the comparison of the occurrence of hypoglycemia in sCTR and eCTR was not conclusive (0.4 vs. 1.6 events/patient, Mann-Whitney U test, P = 0.11) and there was no difference in LBGI (P = 0.17).

Adults versus adolescents. The sCTR study included adolescents with worse control of diabetes as shown by their HbA_{1c} levels and time in near normoglycemia (69.5 ± 4.6 vs. 50.2% ± 9.7, t test P = 0.047); no other significant differences were observed. In terms of system performance, we applied ANOVA analysis with open loop, as

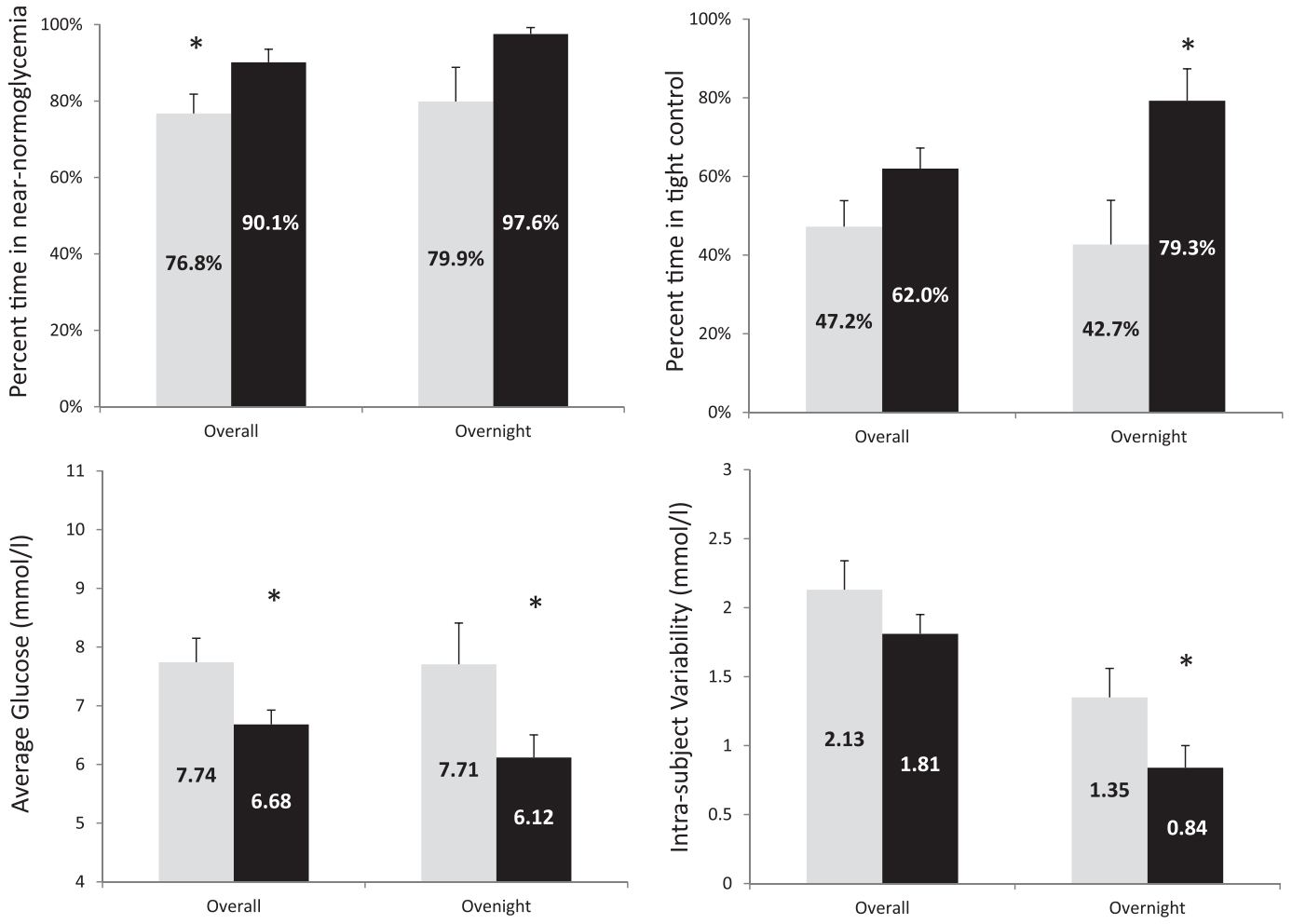

FIG. 4. Primary outcomes of eCTR: Time in near normoglycemia (3.9–10 mmol/L) and tight control (4.4–7.78 mmol/L), average glucose, and intrasubject variability during open- and closed-loop admissions, contrasted by overall and overnight periods. *P < 0.05. Open-loop CSII, gray bar; eCTR, black bar.

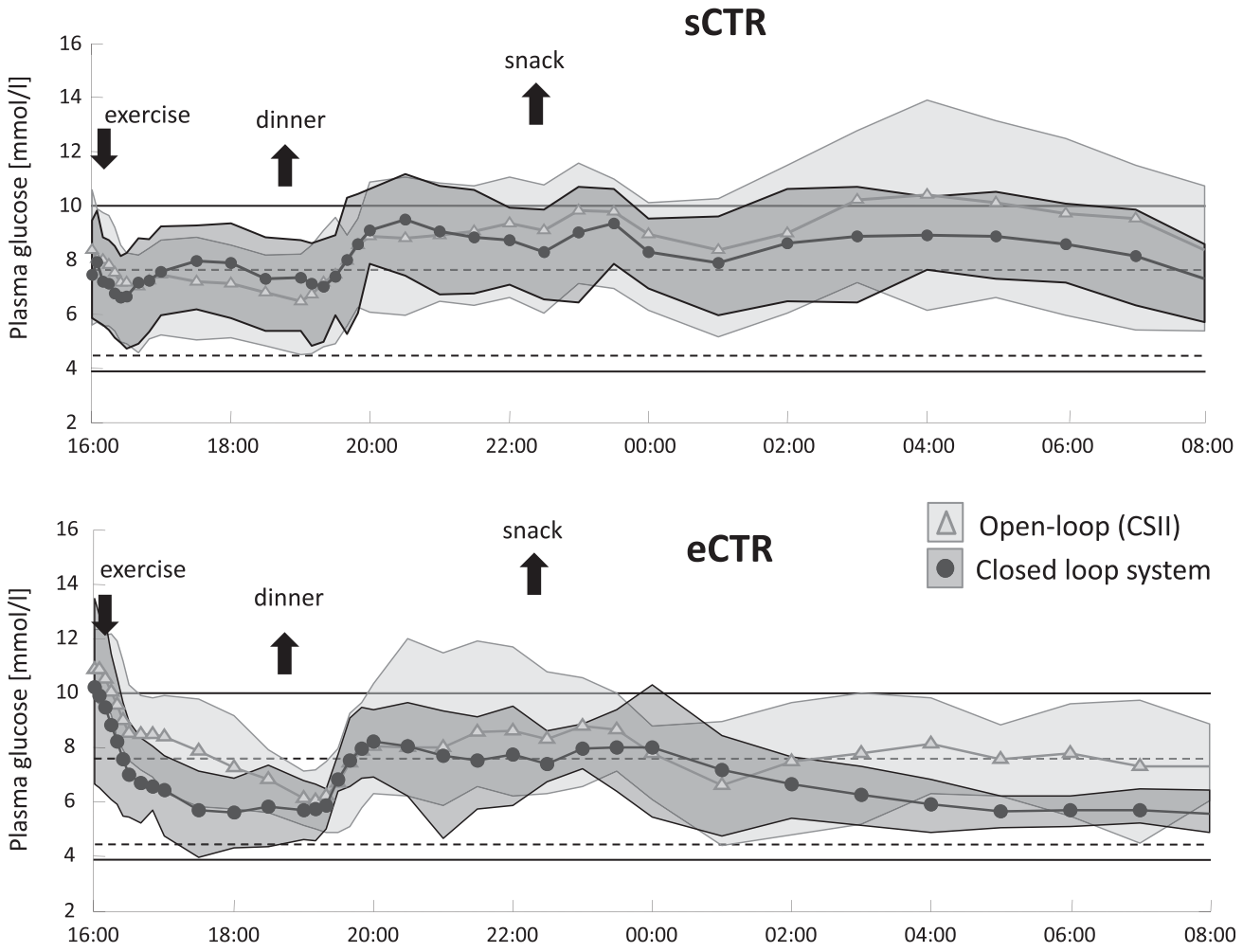

FIG. 5. Mean (curves) and 25–75% quantiles (shaded areas) of plasma glucose for each algorithm comparing open-loop CSII and closed-loop admissions. Glycemic ranges are depicted by the bounds (plain: near normoglycemia; dotted: tight glucose control).

covariate for time in near normoglycemia, and tight control range; hypoglycemia occurrences were compared using Mann-Whitney *U* test. sCTR time in near normoglycemia compared with CSII did not show a significant difference between adolescents and adults (CSII 50.2 to sCTR 65.1% vs. CSII 69.5 to sCTR 81.7%, $P = 0.13$), but time in tight glycemic control was increased in the adult population and not in adolescents (CSII 30.1 to sCTR 21.3% vs. CSII 38.6 to sCTR 50.1%, $P = 0.008$). No difference in the occurrence of hypoglycemia was observed (0.82 to 0.27 vs. 1.29 to 0.5 events/admission, $P = 0.37$).

DISCUSSION

These two randomized crossover studies of CLC in type 1 diabetic patients demonstrate *1*) the feasibility of fully integrated subcutaneous CLC in a clinical setting, *2*) the utility of modular architecture for designing different CLC system functional configurations, *3*) the ability of two CTR algorithms to provide increased safety and effectiveness of glucose control as compared with CSII managed by the patients, and *4*) the ability of CTR to mitigate hypoglycemia even when challenged by exercise, particularly overnight.

In terms of feasibility, we showed that fully integrated CLC can be accomplished in the clinic using Insulet Omnipod and Dexcom Seven Plus (or Abbott Free Style Navigator) CGM connected to a laptop running the APS software and a CTR algorithm. One path toward CLC systems suitable for outpatient use can be charted by our modular approach: starting with a relatively simpler SSM operating alone, then adding more complex range control modules, and ultimately moving to control to target to approximate glycemic excursions in health. In addition to validated algorithmic components, initial outpatient studies will likely require back-end servers and communication tools for remote monitoring and intervention. Finally, to cope with the changing environmental conditions and with the physiological/behavioral changes of the patient, the future ambulatory artificial pancreas will have to adapt to the changes in an individual's biobehavioral parameters over time. Possible methods to cope with changing daily conditions include individual controller calibration strategies and run-to-run control algorithms (31,32), as well as behavioral analysis and profiling of patient lifestyle (33,34). These approaches find their natural application in the upper layer of the modular architecture.

The two CTR systems tested here share the same lower architectural layer (SSM) but differ in the middle layer (range control module). In particular, sCTR is designed as an adjunct to CSII therapy: it operates only when the patient's risk for hypo- or hyperglycemia warrants adjustment of insulin delivery and resumes the usual CSII

treatment when the danger has passed. eCTR includes the same safety module as sCTR but augmented by insulin-on-board constraints (29) and a range control module, based on MPC. eCTR aims to achieve tight glycemic control via take over of patient management of CSII (i.e., it is designed to control basal rate and to leave residual interaction only to trigger premeal insulin boluses, with insulin amount automatically calculated based on an estimate of meal intake).

As intended, sCTR improved patient safety, as shown by a significant decrease in the frequency of hypoglycemic events, and at the same time increased the time spent in near normoglycemia. This improvement was most prominent for patients with suboptimal CSII self-therapy: when we compared patients with below- versus above-median time in near normoglycemia on CSII, we determined that patients in poor control had greater benefits increasing their time in near normoglycemia from 39.5 to 65.4% (P = 0.002), while patients with a better control maintained their time in near normoglycemia (80.9 vs. 82.6%). In other words, sCTR was most beneficial for subjects with poorer glycemic control at baseline.

In eCTR, the combination of a safety and an aggressive range control reduced significantly the average glucose, as well as glucose variability overnight—results not reported to date with CLC (Figs. 4 and 5, upper panels)—and achieved close to 100% time within target range overnight and nearly 80% time spent within the tight range of 4.4–7.8 mmol/L. It is important to note that eCTR reduced simultaneously average glycemia and glucose variability, which suggests that improved glycemic control would be possible using eCTR without concurrent increase in the risk for hypoglycemia.

Previous studies report significant increase in time within target overnight (15) and reduction in glucose variability as shown by a recent across-trial meta-analysis (35). The studies presented here are therefore a step forward in the advancement of CLC, reporting improvement in both average glucose and glucose variability. Despite differences in control architecture and experimental protocol, it is also worthwhile to compare our results with those reported in a 24-h study of CLC using insulin and glucagon without premeal boluses (16). In a first set of experiments that had comparable mean BG (7.8–8.3 mmol/L), 5 out of 11 subjects in that study (44%) experienced hypoglycemia despite glucagon injection (16). Here we show that the SSM was similarly effective in preventing hypoglycemia without glucagon use: in our study 1, a total of 8 out of 25 patients (32%) experienced hypoglycemia during closed loop. Of note, in a second set of experiments, the glucagon system prevented all hypoglycemic events, but at the expense of increasing average glucose to 9.1 mmol/L (16).

It should also be noted that interday metabolic variations could lead to different outcomes in the same patient tested twice. This effect artificially increases variability during statistical analysis and can result in nonsignificant findings, particularly with a small number of subjects (such as in study 2). This limitation is intrinsic to pilot studies and cannot be avoided without multiple repeated admissions, both in open and closed loop for each subject, or without long-term outpatient experiments. Other limitations of the research presented here include short-term hospital-based studies, exact meal timing and balanced food composition, and standardized exercise. While these limitations, to a large extent, are mitigated by the randomized crossover design of our protocols, all of them gradually will be surmounted in subsequent work.

In conclusion, sCTR and eCTR represent sequential modular approaches toward and tightening of automated glycemic control. Therefore, specific clinical applications for each algorithm configuration can be speculated: for example, patients with both poor control and high BG variability, particularly at night, would benefit from using sCTR. In contrast, patients who are in good self-control with CSII, but who wish to further improve their therapy, would be potential candidates for eCTR. In other words, the modular approach to APSs prompts a compelling new concept: assembly from available modules of CLC algorithms tailored to individual patient needs. Further outpatient studies in larger patient groups and with longer duration therefore will be needed to bring CLC into mainstream clinical practice. Nevertheless, we believe that the modular CTR approach proposed here is an important step toward the development of a viable artificial pancreas, a foundation for stepwise deployment of CLC in home-based studies, and of high relevance to the future treatment of type 1 diabetes aiming to improve quality of life and prevention of long-term complications.

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M.B. was the principal investigator (PI) and senior engineer of the UVA clinical trials; designed the protocol; analyzed the sCTR results; contributed to sCTR design and implementation, satellite role in eCTR design and implementation, and modular architecture; and drafted the manuscript. A.F. was the main study physician of MON. D.B. was the main study physician of PAD. S.A. was the senior clinician and main study physician of UVA (ran 9 adults, supervised adolescent protocol) and designed the protocol. L.M. was the senior engineer of eCTR design and implementation. S.P. was the senior engineer of sCTR design and implementation. C.D.M. was the senior engineer of PAD trials and contributed to analysis of eCTR results, design, and implementation and drafted the manuscript. J.P. was the senior engineer during the MON trials. S.D. was the study pediatrician of UVA (ran the 11 adolescents) and participated in pediatric protocol design. S.D.F. was an engineer during the PAD trials and performed eCTR data analysis. C.T. contributed to eCTR design and implementation. C.H.-K. contributed to sCTR design and implementation and satellite-to-eCTR design. E.D. consulted on APS functioning, eCTR design, and modular architecture. H.Z. and F.J.D. consulted on eCTR design and modular architecture. G.D.N. was the senior consultant of eCTR design and contributed to modular architecture. A.A. was the PI of the PAD clinical trial and senior clinician of PAD and drafted the manuscript. C.C. was the PI of the PAD subcontract and senior engineer of eCTR development and contributed to modular architecture and drafted the

manuscript. E.R. was the PI of the MON trials, senior clinician in MON, and PI of the MON subcontract and designed the protocol and drafted the manuscript. B.K. was the overall project PI, PI of the UVA site, and senior engineer of modular architecture and contributed to sCTR/eCTR and protocol design and drafted the manuscript. All authors reviewed and provided edits and comments on manuscript drafts. M.B. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. E.D. has received support from the Animas Corp Advisory Panel. H.Z. has received support from the Animas Corporation Advisory Panel–MannKind Corp Advisory Panel, and research support from Dexcom, Lilly, Insulet, Lifescan Medtronic, and Novo Nordisk. H.Z. serves as a consultant for Roche. No other potential conflicts of interest relevant to this article were reported.

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