

***In silico* simulation of long-term Type 1 diabetes glycaemic control
treatment outcomes**

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Objectives:

To develop a safe and effective protocol for the clinical control of Type 1 diabetes using conventional self-monitoring blood glucose (SMBG) measurements, and multiple daily injection (MDI) with insulin analogues. To develop an *in silico* simulation tool of Type 1 diabetes to predict long-term glycaemic control outcomes of clinical interventions.

Methods:

The virtual patient method is used to develop a simulation tool for Type 1 diabetes using data from a Type 1 diabetes patient cohort ($n=40$). The tool is used to test the adaptive protocol (AC) and a conventional intensive insulin therapy (CC) against results from a representative control cohort. Optimal and suboptimal basal insulin replacement are evaluated as a function of self-monitoring blood glucose (SMBG) frequency in conjunction with the (AC and CC) prandial control protocols.

Results:

In long-term glycaemic control, the AC protocol significantly decreases HbA_{1c} in conditions of suboptimal basal insulin replacement for SMBG frequencies ≥ 6 /day, and reduced the occurrence of mild and severe hypoglycaemia by 86-100% over controls over all SMBG frequencies in conditions of optimal basal insulin.

Conclusions:

A simulation tool to predict long-term glycaemic control outcomes from clinical interventions is developed to test a novel, adaptive control protocol for Type 1 diabetes. The protocol is effective *and* safe compared to conventional intensive

insulin therapy and controls. As fear of hypoglycaemia is a large psychological barrier to glycaemic control, the AC protocol may represent the next evolution of intensive insulin therapy to deliver increased glycaemic control with increased safety. Further clinical or experimental validation is needed to fully prove the concept.

1. INTRODUCTION

Control of Type 1 diabetes is a widely studied and experimented research field. Previously published control methods are diverse, using different routes of insulin administration and glucose measurement. Since the 1970s, the closed loop artificial endocrine pancreas (AEP) has been heralded as the solution (as reviewed in [1]). While no commercial product currently exists, the systems in current clinical use that are likely to constitute the components of an extracorporeal artificial pancreas are the continuous subcutaneous insulin infusion (CSII) pump and a continuous glucose measurement (CGM) device. Advanced control algorithms and methods to ‘close the loop’ have also been widely studied (as reviewed in [2-4]) in spite of early and ongoing limitations in sensors and pumps. Currently, the use of open-loop CGM and/or CSII has resulted in at best, a modest *clinical* advantage over conventional methods of insulin administration or multiple daily injection (MDI) (as reviewed in [5, 6]). Additionally, these systems are only used by a small population of Type 1 diabetics due to high upfront costs, costs of consumables, complexity, and the extensive healthcare infrastructure and support required. Prevalence of CSII use is as low as 2% of the Type 1 diabetes population in the UK and up to 15-20% elsewhere and the US [7].

Hence, there is a more practical and urgent need to address the large majority of the Type 1 diabetes population using conventional glucose measurement i.e. self-monitoring blood glucose (SMBG) and insulin administration i.e. MDI methods, and for whom current conventional or intensive therapies are failing to deliver recommended levels of glycaemic control [8]. In the US, over 50% of diagnosed

diabetics aged 20-64 are deemed ‘out of control’ [9]. The higher accuracy of bedside capillary blood glucose meters [10, 11], and the latest insulin analogues for MDI therapy [12], coupled with better control methods have the potential to provide better care to the majority of outpatient or ambulatory Type 1 diabetics than currently observed. Such techniques must necessarily be simple to implement to ensure broad clinical uptake by the diabetes population.

Previously, a system model of the Type 1 insulin-glucose regulatory system and its identification on a virtual patient cohort has been performed. This study reports the development of a simple and practical adaptive method for control of Type 1 diabetes, and subsequent *in silico* simulation on a virtual patient cohort using the system model developed previously.

3.1 Glucose measurement, insulin type and meals

The control protocols developed and tested in this study aim to treat the broad Type 1 diabetes population using conventional techniques e.g. SMBG and MDI therapy. Hence, the control protocols may only receive discrete glucose data at sparse intervals characteristic of SMBG. Measurement frequencies of 2, 4, 6 8 and 10/day are simulated in this study.

The AIDA on-line² virtual cohort is treated with a range of short-acting, older intermediate/long-acting, or biphasic insulin [13]. In this study, only rapid-acting MI analogues and the basal insulin analogue glargine are used. Insulin analogues have a more physiological and less variable pharmacokinetic profile than traditional insulin

preparations [14] and allow more faithful basal-bolus insulin replacement [15]. Clinically, reduced hypoglycaemia and glycosylated haemoglobin (HbA_{1c}) have been associated with insulin glargine and MI [16-18]. MI injected at the start of meals reduced postprandial glucose excursions compared to regular human insulin injected 30mins prior [18]. In addition, only one daily insulin glargine injection is required for basal insulin replacement [19]. These are the key clinical reasons insulin analogues are chosen. While suboptimal glycaemic control is as much a symptom of poorly-adapted treatment strategy [20] as insulin type, it is logical to begin with the least compromised insulin preparations. The insulin model used in this study is capable of modelling the pharmacokinetic profiles of both MI analogues and insulin glargine [21, 22].

The meal carbohydrate content is assumed known to the patient through carbohydrate counting [23-25]. While the technique is only approximate and can be prone to inaccuracy [26], it remains the key clinical strategy recommended to estimate the glycaemic effect of meals for the purpose of adjusting insulin dosage [8].

3.2 Control methodology

In this study, two prandial insulin treatment protocols, a conventional control protocol (CC) and the adaptive control (AC) protocol developed in this study, are simulated *in silico*. The controls protocol is an unpublished protocol used to treat the AIDA on-line² cohort and is not the AIDA² insulin dosage advisor [27]. The controls group results are *calculated* from the AIDA on-line² patient data (the same data used to

generate the virtual patient profiles for this *in silico* study). Hence, *in silico* simulation is not required for the controls group.

The AIDA on-line² data is a simulation of the patient steady-state response to fixed, daily insulin and dietary stimuli. To make the results of this study comparable, simulations are performed over a period of three days with the same, fixed insulin and dietary stimuli. Plasma glucose, insulin, and meal Ra profiles from the third day are considered steady-state (AIDA assumes the data from the second day are steady state [27]) and are taken as the final result.

For each tested protocol, SMBG frequencies of 2, 4, 6, 8 and 10/day are tested. In addition, a basal insulin titration regimen is used with both protocols to observe the outcome of optimal basal insulin replacement using insulin glargine compared to controls. The target blood glucose is 5mmol/l and a maximum bolus dose of 15U is assumed for both protocols.

3.2.1 Conventional control (CC)

The CC protocol is based on a published IIT [28-30]. The protocol administers a bolus at the start of the meal, $t_{meal,i}$ (where $t_{meal,i}$ is the time of the i th meal). One glucose measurement at the start of the meal \bar{G}_{meal}^i is required to calculate the bolus size. The CC protocol is not adaptive as it uses fixed, suboptimal patient-specific parameters determined from the original AIDA on-line² patient data. Referring to Figure (1), the Carbohydrate-to-Insulin (CIR) ratio is determined for each patient

using the 450 Rule (37 out of the 40 patients in the cohort are treated with regular insulin) [29]. The CIR can also be calculated using Equation (1).

$$\text{CIR [g of carb per U regular insulin]} = \frac{450}{\text{Total Daily Insulin Dose}} \quad \text{Eq. 1}$$

(Figure (1) here)

Referring to Figure (2), an insulin sensitivity factor (ISF) is similarly determined for each patient using the 1500 Rule for regular insulin [30]. The ISF can also be calculated using Equation (2).

$$\text{ISF [mmol/l per U regular insulin]} = \frac{1500}{18 \times \text{Total Daily Insulin Dose}} \quad \text{Eq. 2}$$

(Figure (2) here)

Using the patient CIR and ISF parameters, the CC protocol then calculates the i th prandial insulin dose using Equation (3) assuming that the i th meal carbohydrate count is known from carbohydrate counting.

$$\text{Prandial dose}_i \text{ [U]} = \min(\text{Maximum bolus dose}, \text{Meal dose}_i + \text{Correction dose}_i) \quad \text{Eq. 3}$$

where:

$$\text{Meal dose}_i [\text{U}] = \left(\frac{\text{Meal carbohydrate count}_i}{\text{CIR}} \right)$$

$$\text{Correction dose}_i [\text{U}] = \left(\frac{\bar{G}_{meal}^i - \text{Target blood glucose}}{\text{ISF}} \right)$$

3.2.2 Adaptive control (AC)

The AC protocol utilises an adaptive method to determine the prandial insulin dose. The protocol comprises a twin bolus regimen per meal, with a conservative initial bolus, and an aggressive second bolus to accurately restore glycaemia to basal. The second bolus is administered 90mins after the start of the meal and hence, the first bolus. The first bolus is dosed according to the CC protocol. As such, two glucose measurements are required per meal, $\bar{G}_{meal,1}^i$ and $\bar{G}_{meal,2}^i$ before each bolus, at $t_{meal,i}$ and $t_{meal,i}+90$ (where $t_{meal,i}$ is the time of the i th meal).

This time interval between boluses of 90mins is not arbitrary. In normal individuals, plasma glucose is restored to pre-meal basal levels in approximately 120mins [31] for a normal meal (~1g glucose/kg body weight) and up to 360mins [32] for a very large meal (~4.5g glucose/kg body weight). The 90min time interval chosen ensures minimal postprandial hyperglycaemic exposure. In addition, the time to peak plasma concentration after MI injection ranges from 30-70mins [33], which ensures the second bolus is administered only *after* the plasma insulin concentration from the first bolus has peaked, and approximately 30mins to the peak pharmacodynamic effect of the first bolus [34]. Hence, the 90min time interval is a compromise, injecting the second bolus as late as needed for the first bolus to reach its pharmacodynamic peak for safety, while ensuring that the plasma insulin concentration does not wane, but is

maintained and increased as necessary with the second bolus as a correction to minimise the postprandial glycaemic excursion.

Referring to Equation (4), the AC protocol is adaptive by optimising the patient-specific model parameter S_I to glucose measurement data. Accurately identifying the current patient condition in S_I allows the safer administration of the aggressive insulin bolus. Referring to Equation (5), $G(t)$ for the identification of S_I is linearly interpolated from the glucose measurements $\bar{G}_{meal,1}^i$ and $\bar{G}_{meal,2}^i$. For the i th meal, the identified patient $\bar{S}_{I,i}$ between the measurements at $t_{meal,i}$ and $t_{meal,i}+90$ is used to predict the glycaemic response of the patient in the period $\geq t_{meal,i}+90$ to some prediction end point, t_{pred} (refer Equation (6)).

$$\begin{aligned}
\int_{t_{meal,i}}^{t_{meal,i}+90} \dot{G}(t) dt &= \int_{t_{meal,i}}^{t_{meal,i}+90} [EGP_{0-G} - p_G G(t) - \bar{S}_{I,i} G(t) Q(t) - RGC(t) - CNS + P(t)] dt \\
G(t_{meal,i}) - G(t_{meal,i} + 90) &= \int_{t_{meal,i}}^{t_{meal,i}+90} [EGP_{0-G} - RGC(t) - CNS + P(t)] dt \\
&\quad - p_G \int_{t_{meal,i}}^{t_{meal,i}+90} G(t) dt \\
&\quad - \bar{S}_{I,i} \int_{t_{meal,i}}^{t_{meal,i}+90} G(t) Q(t) dt \\
\bar{S}_{I,i} \int_{t_{meal,i}}^{t_{meal,i}+90} G(t) Q(t) dt &= \int_{t_{meal,i}}^{t_{meal,i}+90} [EGP_{0-G} - RGC(t) - CNS + P(t)] dt \\
&\quad - p_G \int_{t_{meal,i}}^{t_{meal,i}+90} G(t) dt \\
&\quad - [G(t_{meal,i}) - G(t_{meal,i} + 90)]
\end{aligned}$$

Substituting the measurements, $\bar{G}_{meal,1}^i$ and $\bar{G}_{meal,2}^i$

$$\begin{aligned}
\bar{S}_{I,i} \int_{t_{meal,i}}^{t_{meal,i}+90} G(t) Q(t) dt &= \int_{t_{meal,i}}^{t_{meal,i}+90} [EGP_{0-G} - RGC(t) - CNS + P(t)] dt \\
&\quad - p_G \int_{t_{meal,i}}^{t_{meal,i}+90} G(t) dt \\
&\quad - (\bar{G}_{meal,1}^i - \bar{G}_{meal,2}^i)
\end{aligned} \tag{Eq. 4}$$

$$\begin{aligned}
G(t_{meal,i} \leq t \leq t_{meal,i} + 90) &= G(t_{meal,i}) + [G(t_{meal,i} + 90) - G(t_{meal,i})] \left(\frac{t - t_{meal,i}}{90} \right) \\
&= \bar{G}_{meal,1}^i + (\bar{G}_{meal,2}^i - \bar{G}_{meal,1}^i) \left(\frac{t - t_{meal,i}}{90} \right)
\end{aligned}$$

Eq. 5

Then, assuming S_I is constant over the prediction horizon,

$$S_{I,pred}(t_{meal,i} + 90 \leq t \leq t_{pred}) = \bar{S}_{I,i} \quad \text{Eq. 6}$$

Once the patient $\bar{S}_{I,i}$ is known, the second bolus dose is determined iteratively. From Equation (6), a predicted glycaemic response is generated using $S_{I,pred} = \bar{S}_{I,i}$ up to a prediction horizon of 2hrs ($t_{pred} = t_{meal,i} + 90 + 120$). The objective of the iteration is to achieve the 5mmol/l target blood glucose level from the predicted glycaemic response within the 2hr prediction horizon. If $\bar{G}_{meal,2}^i \leq$ target blood glucose level of 5mmol/l or if the iteration results in a zero dose (the predicted glucose response *without* an administered second bolus achieves the target blood glucose level within the prediction horizon) then no second bolus is administered. If the iteration results in a dose exceeding the 15U maximum bolus dose, then the full 15U is administered. In all iterations, using the models means all incoming glucose and insulin from prior MI and insulin glargine doses can be accurately accounted for in determining the correction bolus.

3.3 Basal insulin titration regimen

To optimise basal insulin replacement, a protocol based on the forced-titration regimens of Fritsche et al. [35] and Riddle et al. [36] is used (see Table (1)). Unlike

other basal dosing schemes [37, 38], this regimen has been shown to be clinically effective in a treat-to-target trial [36]. The Fritsche et al. protocol does not specify a dose decrement if hypoglycaemia occurs, but the similar Riddle et al. protocol specifies a small dose decrement of 2-4U/day if the fasting plasma glucose (FPG) is below 3.0mmol/l. Hence, referring to Table (1), the protocol decreases the basal dose by 2U/day if $FPG < 3\text{mmol/l}$ and by 4U/day if $FPG < 2\text{mmol/l}$.

(Table (1) here)

As in Riddle et al. [36], the FPG is assumed to be the pre-breakfast blood glucose level and is closest to the ADA definition of FPG of ‘no caloric intake for at least 8hrs’ [8]. The single daily glargine dose is injected at the last meal of the day instead of bedtime (as in Riddle et al.) as it does not require assumptions about bed times and is unlikely to affect the titration scheme. Unlike Riddle et al., the initial basal dose is chosen to be 80% of the total basal dose from the original patient data, which is recommended for patients changing over to insulin glargine from other basal insulin types [39]. The Riddle et al. initial basal dose of 10U is recommended only for insulin naïve patients and is less suitable for this study [39]. The maximum insulin glargine dose is limited to 80U (hence 80U/day) even though doses up to 100U can be clinically prescribed [39]. In the case of suboptimal basal insulin replacement, the basal insulin therapy from the controls cohort (the AIDA on-line² patient data) is used.

3.4 Location of SMBG measurements

SMBG frequencies of 2, 4, 6, 8 and 10/day are examined. For both the CC and AC protocols, the first SMBG measurement is always located at the start of breakfast (the approximate FPG) to titrate the basal insulin dose according to the Fritsche et al. protocol (see Section 3.5). For the CC protocol, each subsequent SMBG measurement is located at the start of the meal in descending order of meal size. As the AC protocol requires 2 SMBG measurements per meal, the second SMBG measurement is always 90mins after breakfast. Each subsequent *pair* of SMBG measurements is located at the start and 90mins after the start of the meal in descending order of meal size. Thus, additional pairs of measurements occur at lunch/dinner followed by between-meal snacks. Hence, for an equivalent SMBG frequency, the CC protocol covers double the number of meals.

3.5 HbA_{1c} calculation

Glycosylated haemoglobin, HbA_{1c} is one of two clinical assessment techniques for glycaemic control recommended by the ADA [8]. The test assesses glycaemic control over the preceding 2-3 months [40]. Like AIDA [27], the control simulations in this study are for steady-state glucose and insulin stimuli. The resulting steady-state glycaemic response can then be used to calculate an indicative and approximate HbA_{1c} value [41], *if* the control is assumed to be relatively constant over a 2-3 month period. From Rohlfing et al. [41], HbA_{1c} can be defined as a linear function of mean plasma glucose only. Referring to Figure (3) of data reproduced from Rohlfing et al., an HbA_{1c} regression equation can be estimated.

(Figure (3) here)

$$\text{HbA}_{1c} = 0.5\text{MBG} + 2.25 \quad \text{Eq. 7}$$

where

MBG = mean blood glucose concentration [mmol/l]

The MBG is calculated as the arithmetic mean of the 24h simulated glycaemic profile (1min time step). Compared to the HbA_{1c} regression equation in Equation (8) adapted from by AIDA on-line² [42], the Rohlfing et al. equation is more conservative.

$$\text{HbA}_{1c} = 0.6\text{MBG} + 2.87 \quad \text{Eq. 8}$$

The HbA_{1c} value calculated with Equation (7), while approximate and only if the control is assumed to persist for 2-3 months, provides a clinical significant performance metric to the results of this study. In particular, the DCCT [43] and others have shown clinical outcomes as functions of HbA_{1c} , which is a reliable and accepted metric in large intervention trials.

3.6 Summary of simulations performed

4 controllers are simulated. These controllers are:

- AC prandial insulin protocol - optimal basal insulin
- AC prandial insulin protocol - suboptimal basal insulin

- CC prandial insulin protocol - optimal basal insulin
- CC prandial insulin protocol - suboptimal basal insulin

For each controller, SMBG frequencies of 2, 4, 6, 8 and 10/day are simulated, giving 20 simulations in total (5 SMBG frequencies simulated *per* controller type). In addition:

- The controls cohort results *are* calculated from the AIDA on-line² patient data (the same data used to generate the virtual patient profiles for this *in silico* study) and is not the AIDA² insulin dosage advisor [27]. No *in silico* simulation is performed for the controls group.
- Optimal basal insulin replacement is performed using the Fritsche-Riddle basal insulin forced-titration regimen. For suboptimal basal insulin replacement, the basal insulin therapy from the controls cohort (the AIDA on-line² patient data) is used.

HbA_{1c} distributions are compared using a non-parametric, two-tailed Wilcoxon signed-rank test. An asymptotic significance value of <0.05 is considered statistically significant. All calculations and analyses were performed using SPSS[®] (SPSS Inc., Chicago, IL, USA).

2. RESULTS AND DISCUSSION

The results of the *in silico* control simulation are as follows. A sample simulation is shown in Figure (4) of Patient 6 under control by the AC protocol with a SMBG

frequency of 6/day. From this result, a patient specific HbA_{1c} can be calculated for this patient and control scheme.

(Figure (4) here)

4.1 HbA_{1c}

Figures (5-8) show the empirical cumulative distribution function (CDF) of HbA_{1c} for the AC and CC protocols with the controls group for comparison, with and without optimal basal insulin replacement.

(Figure (5-6) here)

Referring to Figure (5) and Table (2), only 52.5% of the controls group cohort have an $HbA_{1c} < 7.0\%$ while 40% had $< 6.5\%$. These thresholds are noteworthy as they are the HbA_{1c} glycaemic goals recommended by the ADA [8] and AACE [44] respectively. Only 22.5% had an $HbA_{1c} < 6\%$ which is the normal HbA_{1c} level. The percentage of the controls cohort that meet the ADA recommended glycaemic goal of $HbA_{1c} \leq 7.0\%$ is in agreement with the figure of 48.9% of the US adult diabetes population being 'in control' [9], which supports the controls group as a realistic representation of the broad diabetes population and its treatment.

(Table (2) here)

4.1.1 Suboptimal basal insulin

Compared to controls, both protocols with suboptimal basal insulin replacement perform significantly better for SMBG frequencies $\geq 4/\text{day}$ and $\geq 6/\text{day}$ for the CC and AC protocols respectively. By design, the CC protocol covers twice as many meals as the AC protocol and this advantage is apparent at lower SMBG frequencies. At higher SMBG frequencies, the AC protocol is able to cover most meals in the day with increased accuracy, outperforming the CC protocol significantly for all SMBG frequencies $\geq 6/\text{day}$. At a SMBG frequency of 6/day, 90% and 72.5% of the cohort meet ADA and AACE clinical recommendations respectively compared to 75% and 60% for the CC protocol.

This result is in agreement with clinical results of long-term control using MI. It has been shown that optimal basal insulin replacement *to* the use of MI is required to achieve maximum benefit [18, 33, 45]. The pharmacokinetic profile of MI enables truer *bolus* insulin replacement than regular human insulin and as such, requires a truer *basal* insulin regiment. Basal insulin regiments developed and optimised to regular insulin boluses will be suboptimal with MI boluses. This is evident for both AC and CC protocols with suboptimal basal insulin replacement, which have non-significant HbA_{1c} to controls for SMBG frequencies less than $\sim 3/\text{day}$.

4.1.2 Optimal basal insulin

With optimal basal insulin replacement, glycaemic control is further enhanced. For a 6/day SMBG frequency, the AC protocol now results in 100% of the cohort controlled to ADA guidelines, 92.5% to AACE guidelines, and 85% have normal HbA_{1c} levels.

However, the difference between CC and AC protocols with suboptimal basal insulin replacement (Figure (7)) is much larger than with optimal basal insulin treatment (Figure (8)). As expected, the AC protocol exceeds the CC protocol for all SMBG frequencies except 2/day. However, only the result from the 8/day SMBG frequency is statistically significant. For AACE and the normal HbA_{1c} thresholds given a 6/day SMBG frequency, the difference between the two protocols is just 2.5% of the cohort or 1 patient.

(Figure (7-8) here)

These results indicate that if basal insulin replacement is optimal, both prandial insulin protocols perform adequately. However, if basal insulin replacement is suboptimal and insulin requirements in the post-absorptive period are not met, then the AC protocol compensates, especially at SMBG frequencies ≥ 6 /day where sufficient measurements exist to cover most of the meals in the day. The HbA_{1c} results are summarised in Figure (9).

(Figure (9) here)

4.2 Hypoglycaemia

The hypoglycaemic level of 3.9mmol/l defined by the ADA is adopted in this study [46] as the mild hypoglycaemic threshold. The glucose level to define severe hypoglycaemia is assumed to be 3mmol/l. Cognitive function is impaired from ~ 3 mmol/l [47, 48], which matches the definition of the ADA for severe

hypoglycaemia as ‘an event requiring assistance of another person to actively administer [resuscitative actions]’ [46]. While these definitions are used globally in this study, it is acknowledged that the hypoglycaemic level and response is complex and patient-specific [49].

4.2.1 CC protocol

Referring to Figures (10-13), the total time spent by the cohort in mild ($t_{hypo,mild}$) and severe hypoglycaemia ($t_{hypo,sev}$) is shown as a percentage. For the controls group, $t_{hypo,mild}$ is 7.7%. From Figure (10) for the CC protocol with suboptimal basal insulin replacement, $t_{hypo,mild}$ is relatively constant over all SMBG frequencies at 4.2-4.9%. For the CC protocol with optimal basal insulin replacement, $t_{hypo,mild}$ decreases with increasing SMBG frequency with the highest $t_{hypo,mild}$ of 8.5% occurring for a SMBG frequency of 2/day. This figure exceeds the controls group (7.7%) and the suboptimal basal insulin CC protocol (4.3%). At a SMBG frequency of 4/day, $t_{hypo,mild}$ is 6.5% compared to 4.5% for the suboptimal basal insulin CC protocol. At a SMBG frequency of 6/day, $t_{hypo,mild}$ is comparable to the suboptimal basal insulin CC protocol (4.5% compared to 4.2%), dropping further to 2.9% compared to 4.9% for the suboptimal basal insulin CC protocol at a SMBG frequency of 10/day.

(Figure (10) here)

Similarly, $t_{hypo,sev}$ is relatively constant at ~1.8% for the CC protocol with suboptimal basal insulin replacement. Like $t_{hypo,mild}$, $t_{hypo,sev}$ under the CC protocol with optimal basal insulin replacement is maximum at 1.2% for a SMBG frequency of 2/day and

decreases to 0.6% for a SMBG frequency of 10/day. For the controls group, $t_{hypo,sev}$ is 3.5%.

In summary, across all SMBG frequencies, $t_{hypo,sev}$ under the optimal basal insulin CC protocol is reduced by 66-83% over controls and by 33-67% over the suboptimal basal insulin CC protocol. However, $t_{hypo,mild}$ is increased at least until a SMBG frequency of 4/day and is decreased for all SMBG frequencies >6/day. Under the CC protocol and with a low SMBG frequency e.g. 2-4/day, the prandial glycaemic excursion especially for the last meal of the day is usually not completely restored to basal.

This failure to reach a basal level overnight is important because it affects the pre-breakfast glucose measurement used for the titration of the basal insulin dose, resulting in an aggressive dose increase and increased mild hypoglycaemia. Fortunately, this problem does not result in increased severe hypoglycaemia and in fact, optimal basal insulin replacement with insulin glargine results in lower occurrences of severe hypoglycaemia across all SMBG frequencies. With SMBG frequencies of 6/day or more, occurrences of both mild *and* severe hypoglycaemia are reduced over controls and the suboptimal basal insulin CC protocol.

4.2.2 AC protocol

Referring to Figure (11) for the AC protocol with suboptimal basal insulin replacement, $t_{hypo,mild}$ is relatively constant over all SMBG frequencies at 4.2-4.4%. For the AC protocol with optimal basal insulin replacement, $t_{hypo,mild}$ decreases with

increasing SMBG frequency with the highest $t_{hypo,mild}$ of 3.1% and 3.2% occurring for SMBG frequencies of 2/day and 4/day respectively. This figure is 60% less than the controls group (7.7%) and 28% less than the suboptimal basal insulin CC protocol (4.4%). At a SMBG frequency of 8/day, $t_{hypo,mild}$ reaches a nadir of 0.7% before increasing to 1.3% for a SMBG frequency of 10/day.

(Figure (11) here)

Similarly, $t_{hypo,sev}$ is relatively constant at ~1.8% for the AC protocol with suboptimal basal insulin replacement. Like $t_{hypo,mild}$, $t_{hypo,sev}$ under the AC protocol with optimal basal insulin replacement is maximum at 0.6% for SMBG frequencies of 2/day and 4/day but decreases to zero percent for SMBG frequencies ≥ 6 /day.

In summary, across all SMBG frequencies, $t_{hypo,sev}$ under the AC protocol with optimal basal insulin replacement is reduced by 86-100% over controls and by 72-100% over the AC protocol with suboptimal basal insulin replacement. Across all SMBG frequencies, $t_{hypo,mild}$ under the AC protocol with optimal basal insulin replacement is reduced by 58-91% over controls and 27-84% over the AC protocol with suboptimal basal insulin replacement. Prandial glycaemic excursions are more completely restored to basal under the AC protocol even with a low SMBG frequency. This results in a more accurate pre-breakfast glucose measurement for basal insulin titration on the forced-titration regimen with lower resultant mild and severe hypoglycaemia.

4.2.3 Summary of hypoglycaemia results

Referring to Figure (12) for optimal basal insulin replacement, the AC protocol outperforms the CC protocol in hypoglycaemia occurrence over all SMBG frequencies. Given suboptimal basal insulin replacement, occurrence of hypoglycaemia both mild and severe is similar between the two protocols (see Figure (13)). The results of this comparison are similar to that of HbA_{1c} whereby the advantage of the AC protocol is most apparent in conditions of poor basal insulin replacement.

Contrary to the DCCT [43], hypoglycaemia did not increase under the conventional IIT (CC protocol) in this study. In both cases of suboptimal and optimal basal insulin replacement, severe hypoglycaemia is reduced for all SMBG frequencies compared to controls. This result is in excellent agreement with the study by Sämann et al. [20] where implementation of a flexible IIT protocol improved glycaemic control without increased risk of severe hypoglycaemia. The protocol in the Sämann et al. study consists of a structured inpatient training course, implemented into routine care with continuous quality assurance on a national level. Hence, it is reasonable to assume high patient protocol adherence and that the conditions in this study are similar to that inherent of the *in silico* simulation, which assumes full patient adherence.

(Figure (12-13) here)

4.3 SMBG frequency

The frequency of SMBG has been known to affect glycaemic control, as reviewed in [50]. For Type 1 diabetes, the ADA [8] and AACE [44] both recommend a SMBG frequency $\geq 3/\text{day}$ and in a study by Monnier et al. [51], 5- to 8-point daily glucose monitoring is recommended. Davidson et al. [52] has modelled HbA_{1c} and SMBG with Equation (9).

$$\text{HbA}_{1c} = 5.99 + \frac{5.32}{(\text{tests per day} + 1.39)} \quad \text{Eq. 9}$$

Referring to Figure (14), the data from Davidson et al. is reproduced with the *median* cohort HbA_{1c} of this study for the various protocols and basal insulin replacement regimens.

The Davidson et al. curve follows closely the suboptimal basal insulin CC protocol. This result supports the validity of the *in silico* simulation, which produces a similar HbA_{1c} simulating a conventional IIT under suboptimal basal insulin replacement. With SMBG frequency $>4/\text{day}$, the suboptimal basal insulin AC protocol reduces the median HbA_{1c} over the CC protocol under the same basal insulin replacement. Both protocols with optimal basal insulin replacement result in a normal median HbA_{1c} even at a low SMBG frequency of $2/\text{day}$ although the AC protocol results in marginally lower HbA_{1c} for all SMBG frequencies $\geq 6/\text{day}$. This result also implies that clinically, poor glycaemic control is mainly a result of suboptimal basal insulin replacement. As shown in Section 4.1.2 basal insulin replacement has the single, most significant effect on HbA_{1c} , much more so than the difference between AC and CC prandial insulin protocols.

(Figure (14) here)

The forced-titration regimen of basal insulin dosing has been found to be safe only if sufficient SMBG and consequently, prandial control is applied in order for the assumed FPG value to be accurate. The basal insulin forced-titration regimen relies on a single, pre-breakfast FPG value and if a patient is poorly controlled prandially, the assumed FPG value is likely to be influenced by the postprandial excursion from the previous night. From this study, this minimum SMBG frequency is approximately ~6/day for a conventional IIT (CC protocol). With the AC protocol, the SMBG frequency does not present a safety issue regardless of basal insulin replacement.

Referring to Table (2), the suboptimal basal insulin CC protocol (a conventional IIT) and a SMBG frequency of 4/day results in 60% of the cohort controlled to ADA guidelines, and 25% to normal HbA_{1c} levels. With 6- or 8-point daily glucose monitoring, these figures are 75.0% and 32.5% respectively. Hence, control with the minimum ADA recommended SMBG frequency, or even the Monnier et al. daily 8-point measurements is unsatisfactory if the protocol implemented is a conventional IIT with suboptimal basal insulin replacement. From this study, glycaemic control with the suboptimal basal insulin CC protocol saturates at a SMBG frequency of 6/day with 75% of the cohort meeting ADA guidelines. Hence, a SMBG frequency of 6/day should be the minimum for a conventional IIT with a suboptimal basal insulin regimen.

With optimal basal insulin replacement, the adaptive AC protocol with a SMBG frequency of 4/day results in 97.5% of the cohort controlled to ADA guidelines, and 82.5% to normal HbA_{1c} levels. In addition, mild hypoglycaemia is reduced by 27% and severe hypoglycaemia by 50% in comparison to the suboptimal basal insulin CC protocol. With optimal basal insulin replacement, the CC protocol produces similarly excellent glycaemic control but mild hypoglycaemia is increased 103% compared to the AC protocol. Fear of hypoglycaemia is frequently cited for deliberate insulin under-dosing, both prandial and basal [35, 53]. Hence, the adaptability of the AC protocol may represent the next evolution of IIT to deliver increased glycaemic control with increased safety.

3. CONCLUSIONS

An *in silico* simulation tool is presented that utilises an extended model of glucose kinetics, and the novel application of a subcutaneous insulin pharmacokinetic model. The virtual patient cohort and its default control protocol (the data of which is used for *in silico* simulation) can be considered a good representation of the broad diabetes population. The simulation tool is used to develop a robust, adaptive protocol for prandial insulin dosing.

In virtual trial simulations, the adaptive protocol has been shown to significantly decrease HbA_{1c} in conditions of suboptimal basal insulin replacement for SMBG frequencies ≥ 6 /day and reduce the occurrence of mild and severe hypoglycaemia by 86-100% over controls over all SMBG frequencies in conditions of optimal basal insulin. When a conventional IIT is employed in conditions of suboptimal basal

insulin, the increase in cohort compliance to clinical control guidelines saturates at a SMBG frequency of 6/day. In addition, under conventional IIT, the basal insulin forced-titration regimen requires a minimum SMBG frequency of 6/day to safely titrate the basal dose without increased hypoglycaemia. The overaggressive basal dose titration with a conventional IIT at lower SMBG frequencies is likely to be caused by uncorrected postprandial hyperglycaemia from the previous night, resulting in an erroneous assumed FPG used for dose titration.

With a SMBG frequency of 4/day and optimal basal insulin replacement, 97.5% of the cohort can be controlled to ADA clinical guidelines using the adaptive protocol, a result similar to a conventional IIT but which has 103% more mild hypoglycaemia. As fear of hypoglycaemia is a large psychological barrier to glycaemic control, the AC protocol may represent the next evolution of IIT that can deliver increased glycaemic control with increased safety. Further clinical or experimental validation is needed to fully prove the concept.

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DISCLOSURES

None recorded.

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FIGURES

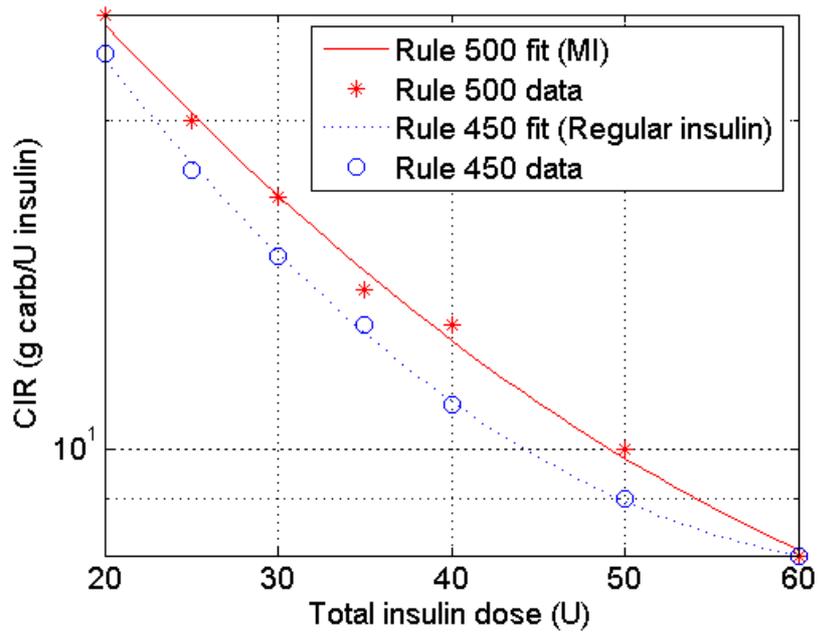


Figure 1 : The carbohydrate-to-insulin (CIR) ratio is determined for each patient using the 450 Rule for regular insulin (37 out of the 40 patients in the cohort are treated with regular insulin with the rest on biphasic insulin). Data reproduced from [29]

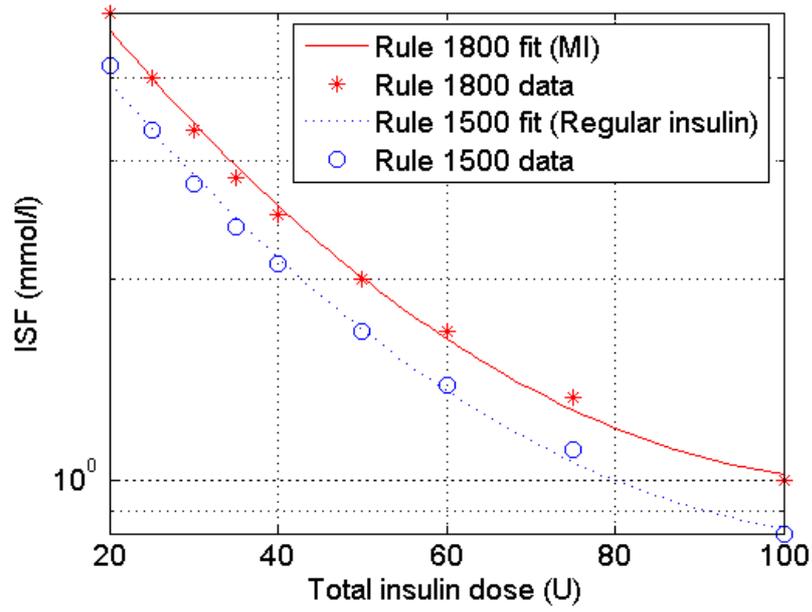


Figure 2 : The insulin sensitivity factor (ISF) is determined for each patient using the 1500 Rule for regular insulin. Data reproduced from [30]

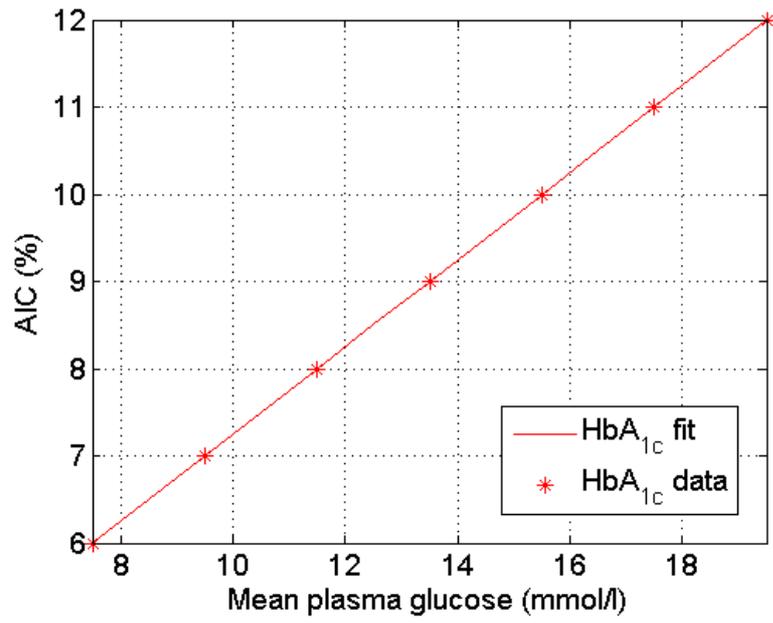


Figure 3: Estimating HbA_{1c} from mean plasma glucose with linear regression. Data reproduced from Rohlfing et al. [41]

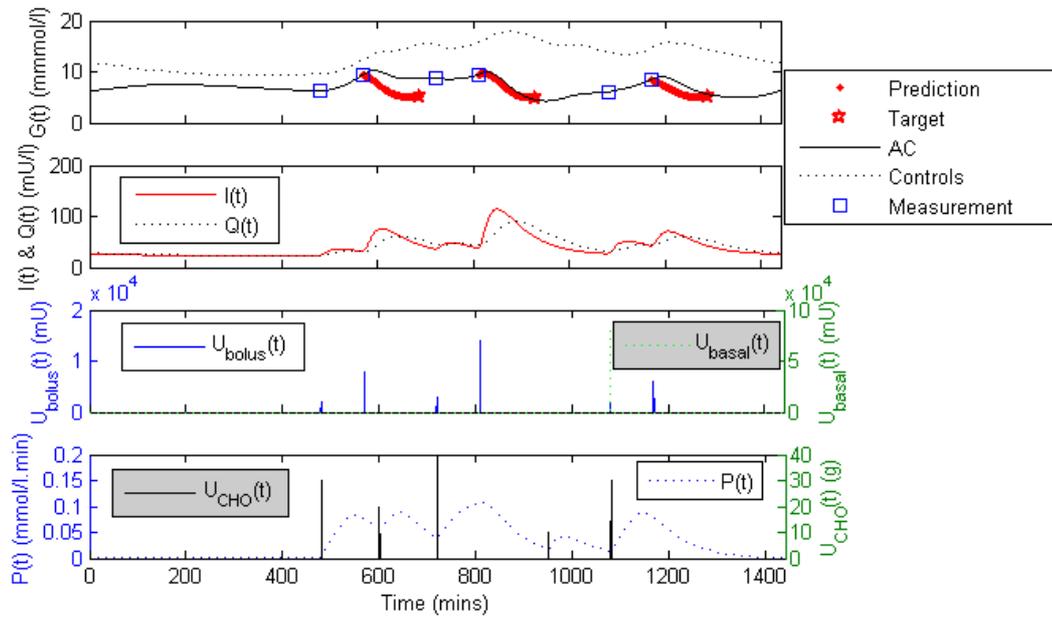


Figure 4: A sample *in silico* simulation of Patient 6 under control by the AC protocol with a SMBG frequency of 6/day

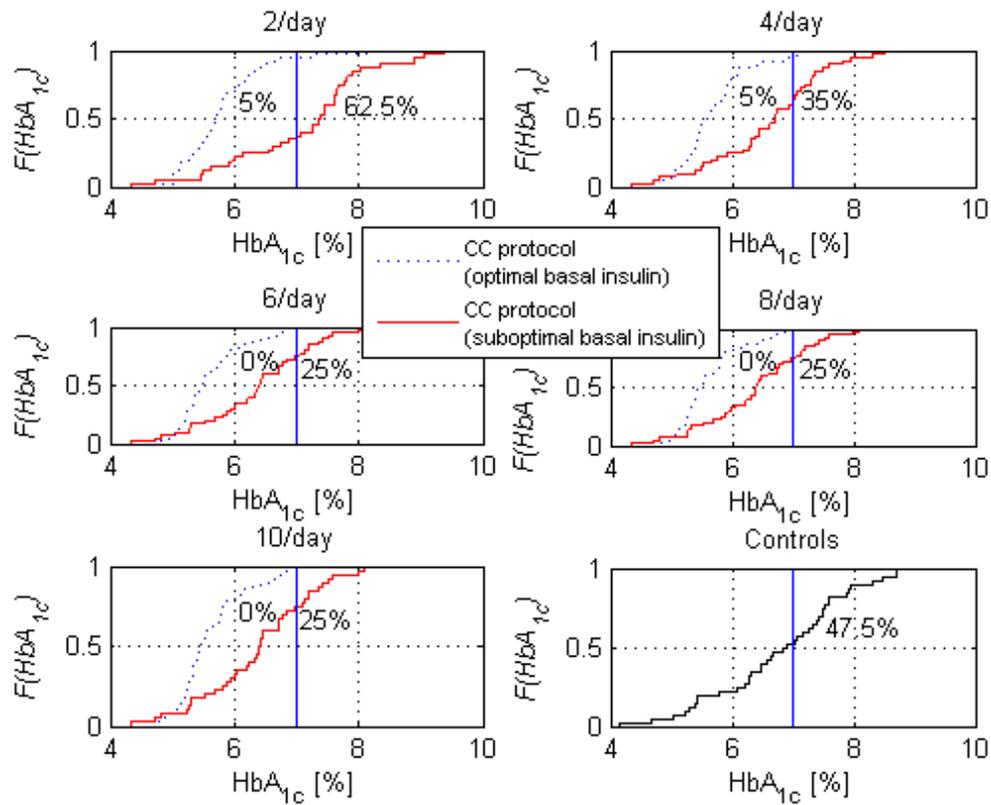


Figure 5: Empirical cumulative distribution function (CDF) of HbA_{1c} for the CC protocol with optimal and suboptimal basal insulin replacement compared to the controls group. The ADA recommended glycaemic control level as measured by HbA_{1c} ≤ 7% is shown with the percentage time spent above the threshold shown for each case.

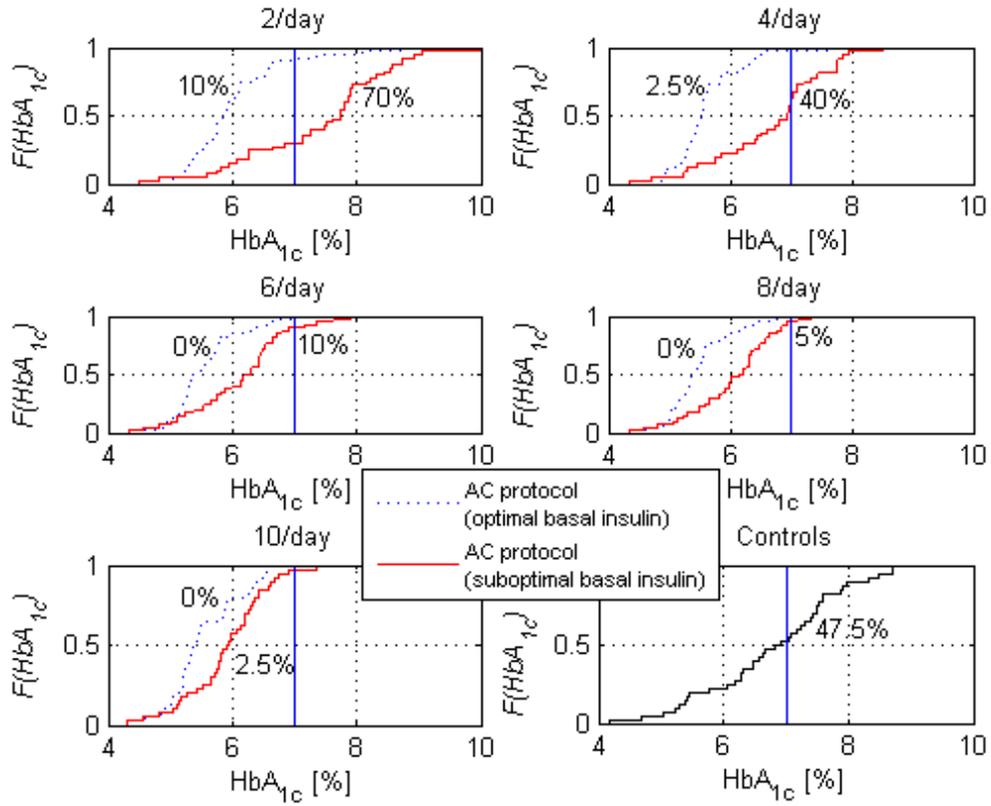


Figure 6: Empirical cumulative distribution function (CDF) of HbA_{1c} for the AC protocol with optimal and suboptimal basal insulin replacement compared to the controls group. The ADA recommended glycaemic control level as measured by HbA_{1c} ≤ 7% is shown with the percentage time spent above the threshold shown for each case.

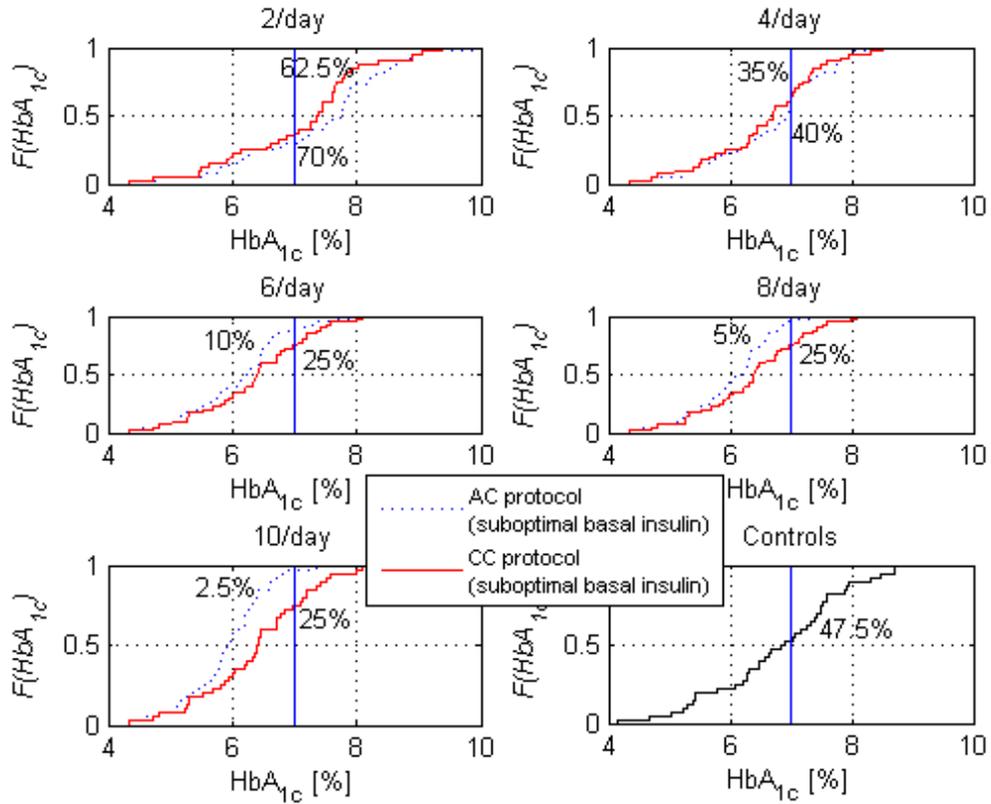


Figure 7: Empirical cumulative distribution function (CDF) of HbA_{1c} for both AC and CC protocols with suboptimal basal insulin replacement compared to the controls group. The ADA recommended glycaemic control level as measured by HbA_{1c} ≤ 7% is shown with the percentage time spent above the threshold shown for each case.

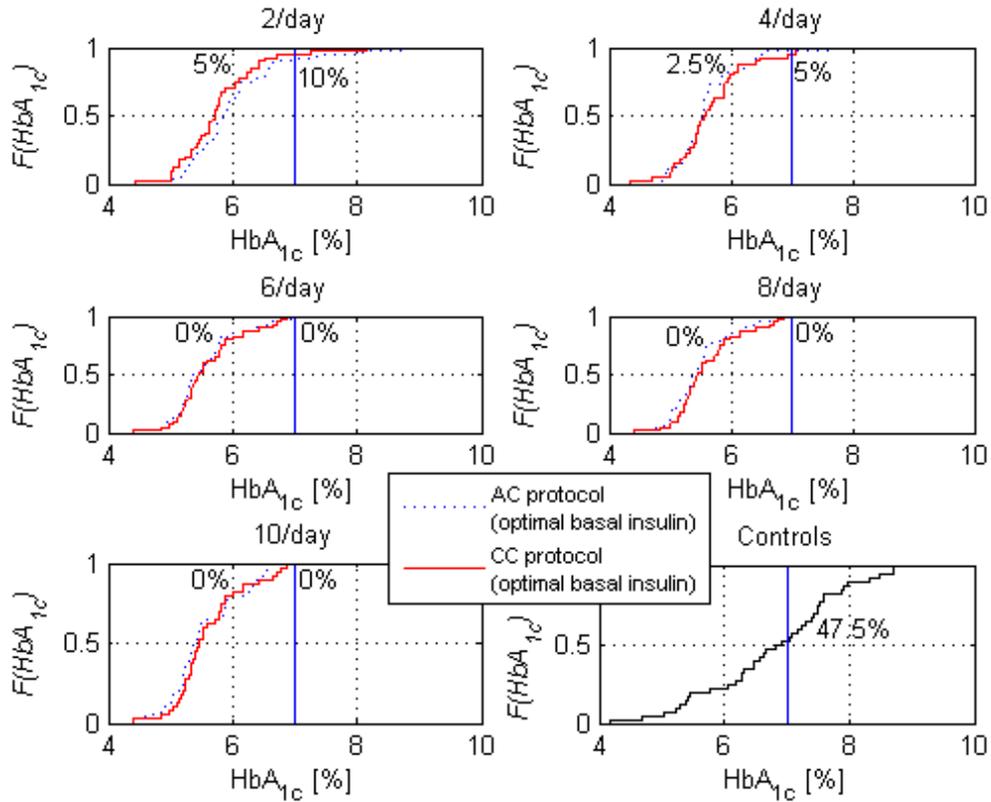


Figure 8: Empirical cumulative distribution function (CDF) of HbA_{1c} for both AC and CC protocols with optimal basal insulin replacement compared to the controls group. The ADA recommended glycaemic control level as measured by $HbA_{1c} \leq 7\%$ is shown with the percentage time spent above the threshold shown for each case.

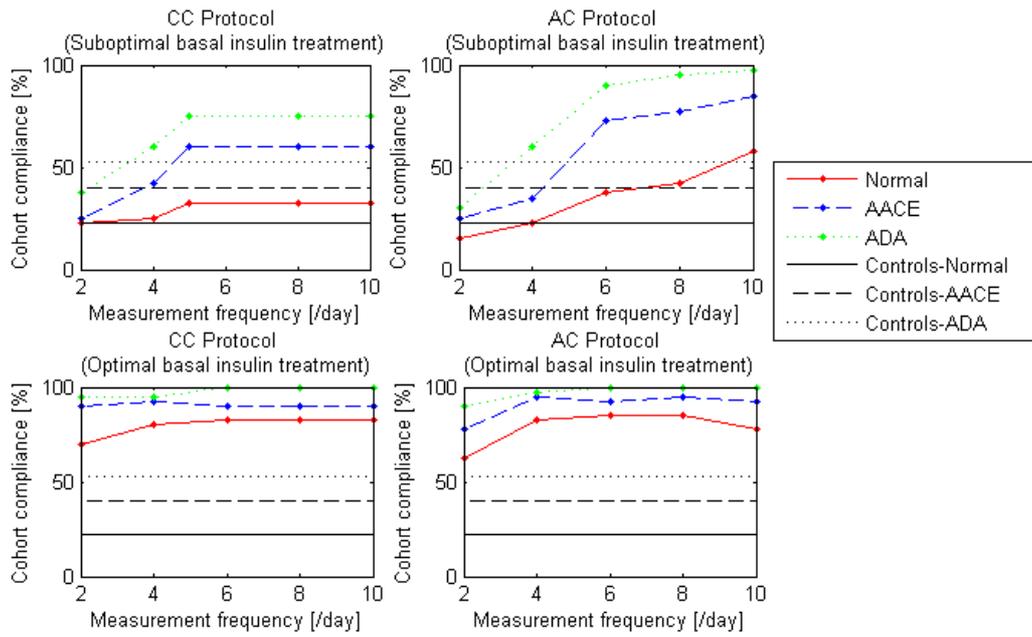


Figure 9: The cohort percentage controlled to clinically relevant HbA_{1c} levels (as recommended by the ADA [8] and AACE [44]) as compared to the controls group. The normal HbA_{1c} level of 6.0% is shown for comparison

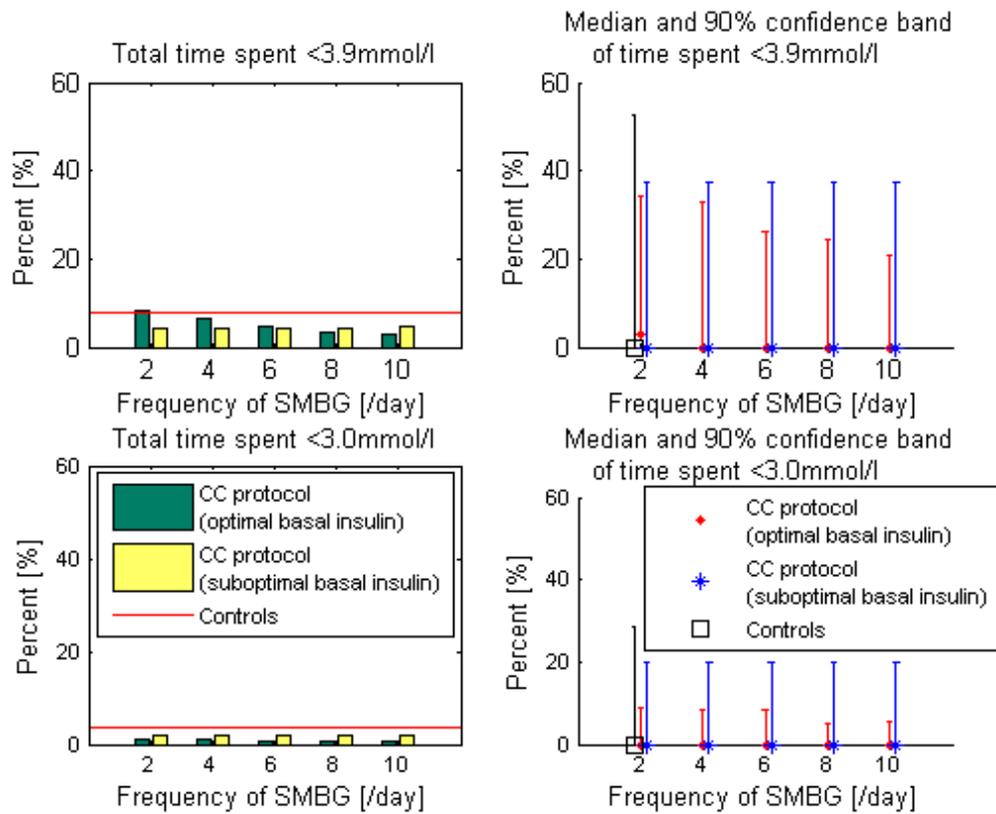


Figure 10: Total time spent by the cohort, and the cohort median and 90% confidence band for the time spent in mild and severe hypoglycaemia under the CC protocol in conditions of optimal and suboptimal basal insulin replacement

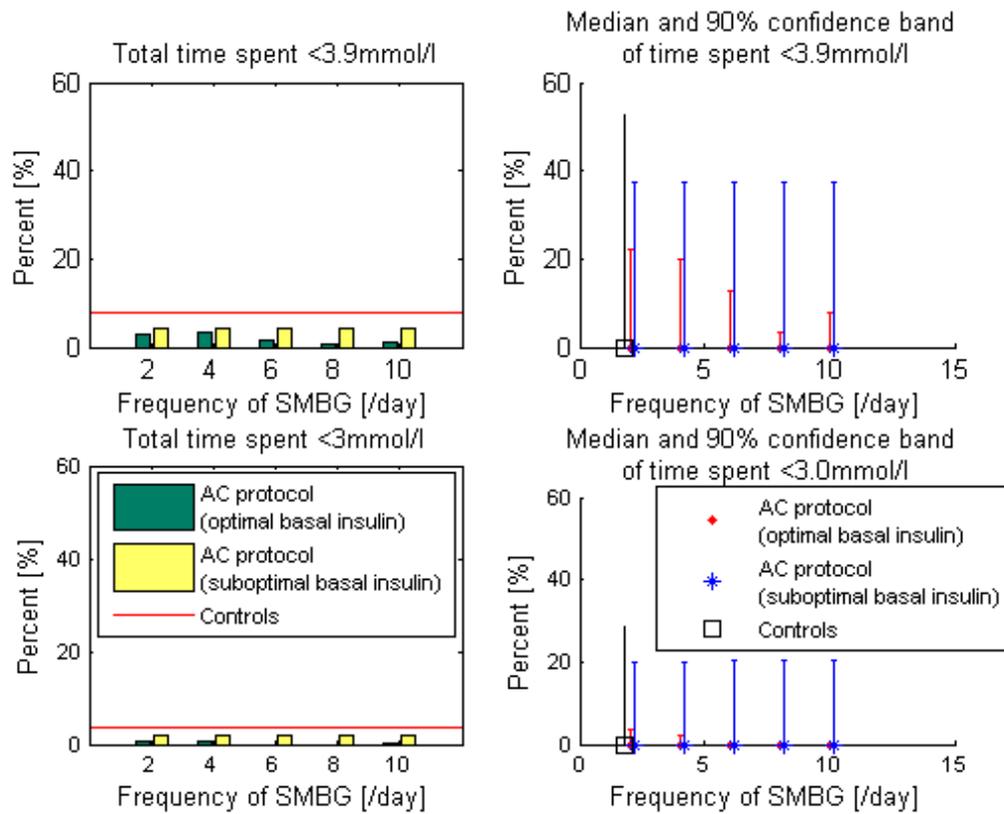


Figure 11: Total time spent by the cohort, and the cohort median and 90% confidence band for the time spent in, mild and severe hypoglycaemia under the AC protocol in conditions of optimal and suboptimal basal insulin replacement

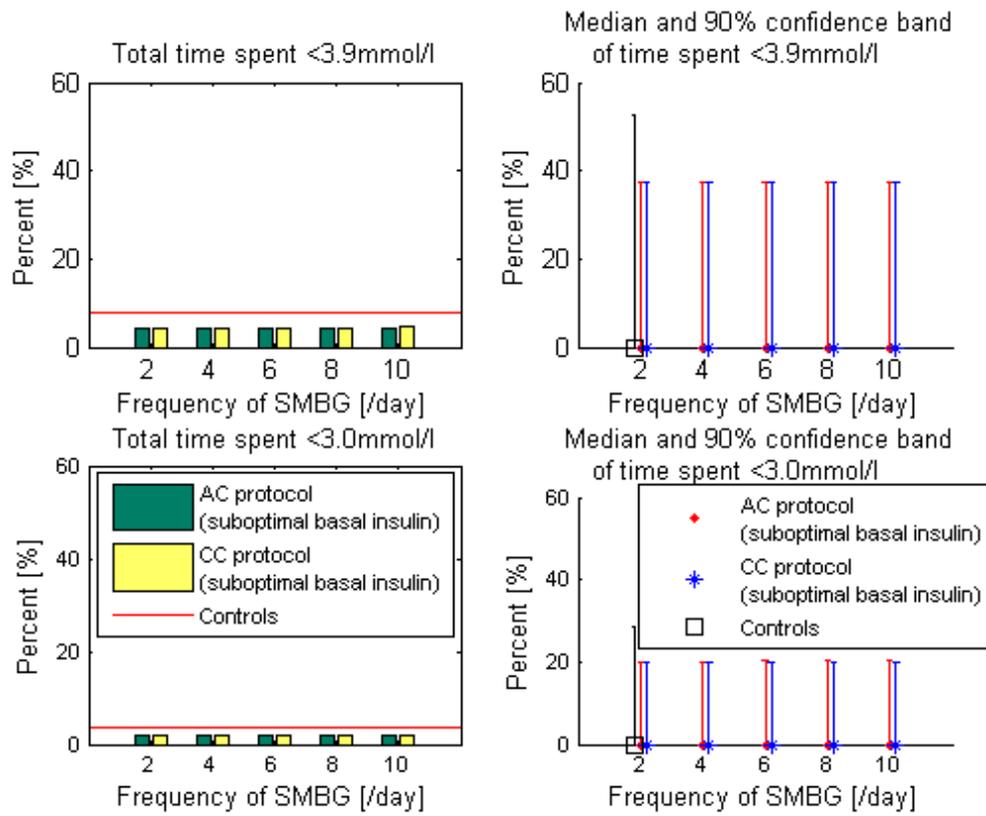


Figure 12: Total time spent by the cohort, and the cohort median and 90% confidence band for the time spent in mild and severe hypoglycaemia under AC and CC protocols and suboptimal basal insulin replacement

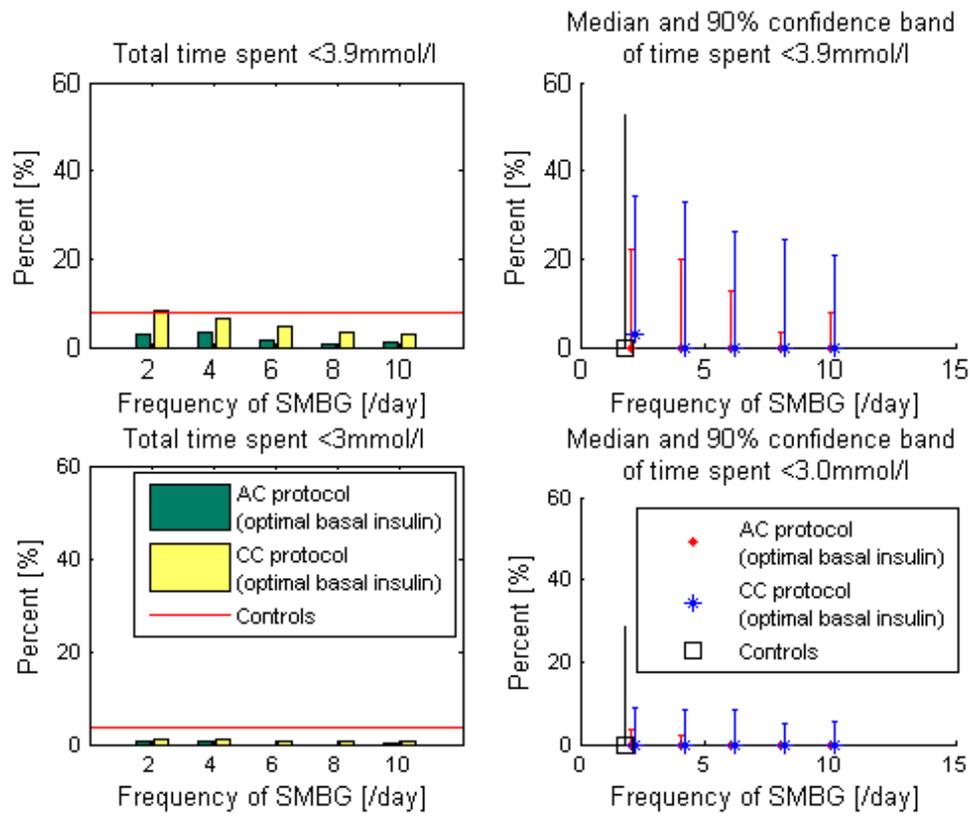


Figure 13: Total time spent by the cohort, and the cohort median and 90% confidence band for the time spent in mild and severe hypoglycaemia under AC and CC protocols and optimal basal insulin replacement

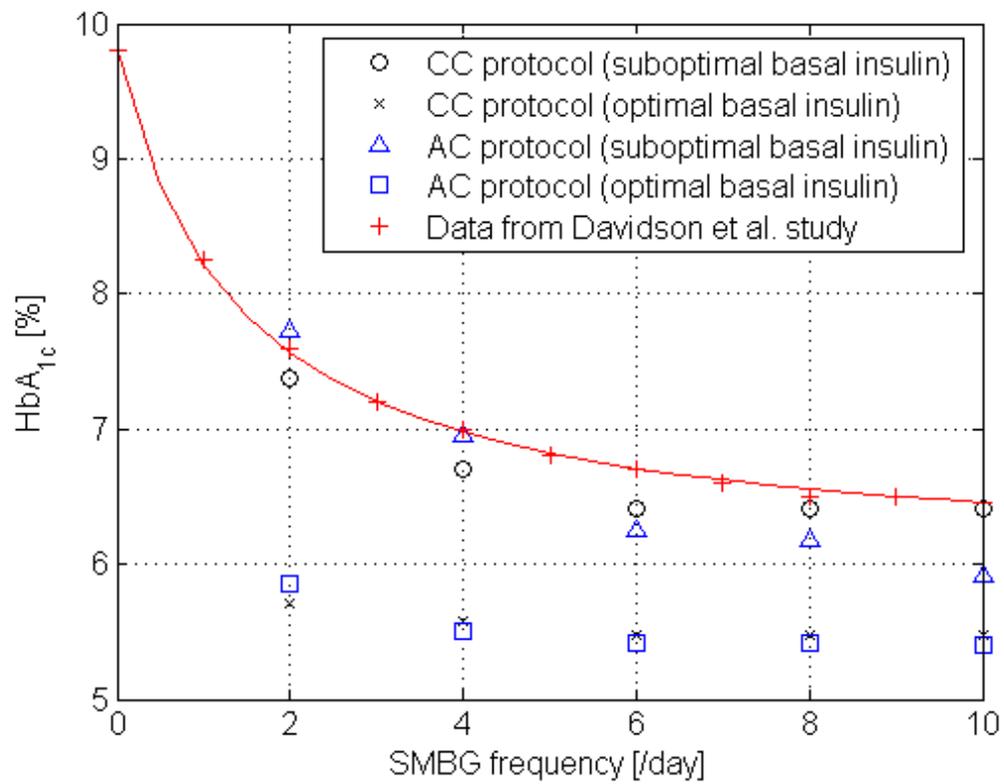


Figure 14: Predicted HbA_{1c} data from Davidson et al. [52] and the *median* cohort HbA_{1c} of this study vs. SMBG frequency. The Davidson et al. curve follows approximately the suboptimal basal insulin CC protocol

TABLES

Table 1: The basal insulin dosing regimen used to optimise the single, daily insulin glargine dose based on the forced-titration regimens of Fritsche et al. [35] and Riddle et al. [36]. This regimen incorporates a dose decrement if hypoglycaemia occurs which the Riddle et al. protocol does not specify explicitly. Unlike Riddle et al., the initial basal dose is chosen to be 80% of the total basal dose from the AIDA² on-line cohort data, which is recommended for patients changing over to insulin glargine from other basal insulin types [39]

Fasting plasma glucose (FPG) [mmol/l]	Initial dose equivalent to 80% of total basal dose	
	Increment in glargine dose (U/day)	Decrement in glargine dose (U/day)
≥10.0	8	
≥7.8 and <10.0	6	
≥6.7 and <7.8	4	
≥5.6 and <6.7	2	
≥3.0 and <5.6		
≥2.0 and <3.0		2
<2		4

Table 2: Summary of the cohort percentage controlled to ADA [8] and AACE [44] glycaemic control recommendations, and to normal HbA_{1c} levels. The percentage of the controls group controlled to ADA recommended HbA_{1c} (52.5%) is in excellent agreement with the figure of 48.9% of the US adult diabetes population being ‘in control’ [9]

			HbA _{1c} [%]		
			<6.0	<6.5	<7.0
Basal protocol type	Prandial protocol type	SMBG frequency [/day]			
Controls			22.5	40.0	52.5
Controls (suboptimal)	CC	2	22.5	25.0	37.5
		4	25.0	42.5	60.0
		6	32.5	60.0	75.0
		8	32.5	60.0	75.0
		10	32.5	60.0	75.0
	AC	2	15.0	25.0	30.0
		4	22.5	35.0	60.0
		6	37.5	72.5	90.0
		8	42.5	77.5	95.0
		10	57.5	85.0	97.5
Forced-titration regimen (optimal)	CC	2	70.0	90.0	95.0
		4	80.0	92.5	95.0
		6	82.5	90.0	100.0
		8	82.5	90.0	100.0
		10	82.5	90.0	100.0
	AC	2	62.5	77.5	90.0
		4	82.5	95.0	97.5
		6	85.0	92.5	100.0
		8	85.0	95.0	100.0
		10	77.5	92.5	100.0