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ORIGINAL RESEARCH ARTICLE

Health Economic Evaluation of a Strict Glucose Control Guideline Implemented Using Point-of-Care Testing in Three Intensive Care Units in The Netherlands

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Abstract

Background Point-of-care testing of blood glucose (BG-POCT) is essential for safe and effective insulin titrations in critically ill patients under glucose control with insulin. The costs associated with this practice are considered substantial, especially when more frequent blood glucose (BG) testing is needed, as with more strict glucose control (SGC) aiming for lower BG levels.

Objective The objective of this study was to estimate, from a hospital perspective, the incremental cost effectiveness of an SGC guideline, aiming for BG levels of 4.4–6.1 mmol/L, compared to the situation before implementation of that guideline (aiming for BG levels <8.3 mmol/L), both using BG–POCT.

Methods This is a secondary analysis of a guideline implementation project aiming for implementation of a guideline of SGC in three intensive care units in The Netherlands. A Markov model including the four health states 'target glucose', 'hyperglycaemia' (defined as BG levels >6.1 mmol/L), 'hypoglycaemia' (defined as BG levels <4.4 mmol/L) and 'in-hospital death' was developed to compare expected costs, number of patients within target and number of life-years saved before and after implementation of the SGC guideline. The effectiveness estimates are based on empirical data from 3195 patients 12 and 24 months before and after implementation of the guideline, respectively. All costs have been converted to price year 2013, and are estimated based on hospital data, the literature and available price lists.

Results The number of BG–POCT increased from 4.8 [interquartile range (IQR) 2.6–6.7] to 8.0 [IQR 4.1–11.2] per patient per day, accruing 58 % higher costs for BG–POCT (€13.56 vs. €8.57 per patient) in the SGC protocol versus the situation before implementation. When taking total hospital costs and clinical effects into account, implementation of the SGC guideline increased total hospital costs per patient by 1.8 %, i.e. €355 (from €20,617 to €20,972) during the inpatient stay, while the number of

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patients in target glucose levels increased by 1.4 % (i.e. from 881 to 895 per 1000 patients). This translates to an incremental cost-effectiveness ratio of €25 per additional patient within the target glucose level. The model outcomes are most sensitive to changes in ICU length of stay. *Conclusion* The increase in the number of patients and time within target glucose levels is achieved with a small increase in total direct hospital costs.

Key Points for Decision Makers

Frequent monitoring of the blood glucose level with point-of-care testing (POCT) is commonly seen as a prerequisite for efficient and safe insulin infusion in the intensive care unit (ICU) setting, yet its costs are typically considered as substantial.

This is the first study that estimates the total opportunity costs of a strict glucose control (SGC) guideline, taking both the costs of glucose POCT into account as well as the downstream costs, and relating this to the effectiveness of treatment defined as the number of patients in target glucose levels.

Implementation of the SGC guideline in ICU patients is expected to lead to an increase of 14 (out of 1000) patients in target glucose per 30-min cycle, while total hospital costs increase by 1.8 %.

1 Introduction

Point-of-care (POC) testing (POCT), defined as medical testing at or near the bedside, usually shortens the turnaround time of test results allowing faster responses [1]. It can effectively facilitate more frequent blood glucose (BG) testing as part of a strict glucose control (SGC) guideline, but comes at an additional cost compared to central laboratory based testing. [2]. POCT-associated costs, however, should not be considered in isolation, but balanced against their potential treatment benefits, which may even translate into potential cost savings elsewhere in the patient pathway.

In intensive care units (ICUs) BG monitoring is performed with POCT devices (BG-POCT) [3]. Notably, frequent monitoring of the BG level with POCT is commonly regarded as a prerequisite for efficient and safe insulin infusion [4]. Even with BG control aiming at higher levels than those used in the original trials of so-called SGC, many patients need insulin during their ICU stay [5]. This SGC guideline aims for BG levels of 4.4–6.1 mmol/L, while in the situation before implementation of that guideline aimed for BG levels of <8.3 mmol/L. However, it was found that introduction of these SGC guidelines increased the incidence of hypoglycaemia [6]. Recently, several studies reported that hypoglycaemia in critically ill patients is associated with an increase in the duration of ICU stay and risk of mortality [7–10].

The objective of this study was thus to estimate, from a hospital perspective, the incremental cost-effectiveness of an SGC guideline that aims for BG levels of 4.4–6.1 mmol/L in three ICUs in The Netherlands, and is implemented using BG-POCT.

2 Methods

2.1 Analytical Framework

We developed a Markov model to estimate the cost effectiveness of an SGC guideline. The model simulates a hypothetical cohort of 1000 patients, based on input data from a previous study about the effects of implementation of the guideline and additional data sources where necessary [11]. The study included a total of 3195 patients, admitted to the mixed medical–surgical ICUs of three community hospitals in The Netherlands. Patient data of the 12 months preceding guideline implementation (1295) to patient data of 24 months after implementation (2100) were compared. Missing data were handled by multiple imputation using SPSS® 20, IBM Corp, Armonk, NY, USA.

The model evaluation includes those costs and effects relevant from a hospital perspective. The time horizon of the analysis equals the duration of a patient's hospital stay, on average 17 days. Since those hospitalisation episodes last on average less than 1 year, discounting is not required. A summary of all input variables and data sources used is provided in Tables 1 and 2.

In the year before implementation of the SGC guideline (2008), BG levels were aimed at <8.3 mmol/L, in line with the 2004 Surviving Sepsis Campaign guideline [12]. Nurses administered insulin either intravenously or subcutaneously following BG measurements at the bedside or in a central laboratory using venous, capillary or arterial blood samples. Recommendations in the guideline were only loosely defined, including timing of BG measurements. Following implementation of the SGC guideline, BG levels were aimed at the range between 4.4 and 6.1 mmol/L, in line with the original studies of SGC in Leuven, Belgium [13–15]. ICU nurses administered insulin via a central venous line using an accurate syringe pump. BG measurements were performed every 4 h and more frequently as deemed necessary by attending nurses.

Table 1 Overview of effectiveness parameters. This table shows the transition probabilities for switching between the four health states (target glucose, hyperglycaemia, hypoglycaemia, and death), the write-off period for the point-of-care testing glucose analyser, the number of point-of-care tests of blood glucose performed as well as the time spent per analysis, and the duration of hospital stay and accompanying treatment. For all transitions to target glycaemia, the standard error was estimated based on the dataset of the three hospitals

Variable	Mean (SE)		References
	Pre-SGC	SGC	
Transition probability target glycaemia to target glycaemia	0.999550 (0.000450)	0.999537 (0.000463)	[11]
Transition probability target glycaemia to hypoglycaemia[a]	0.000012 (0.000012)	0.000082 (0.000082)	[11]
Transition probability target glycaemia to hyperglycaemia[a]	0.000127 (0.000127)	0.000110 (0.000110)	[11]
Transition probability target glycaemia to in-hospital death[a]	0.000310 (0.000310)	0.000271 (0.000271)	[11]
Transition probability hypoglycaemia to target glycaemia	0.999594 (0.000406)	0.999556 (0.000444)	[11]
Transition probability hypoglycaemia to hypoglycaemia[a]	0.000005 (0.000005)	0.000073 (0.000073)	[11]
Transition probability hypoglycaemia to hyperglycaemia[a]	0.000013 (0.000013)	0.000028 (0.000028)	[11]
Transition probability hypoglycaemia to in-hospital death[a]	0.000388 (0.000388)	0.000342 (0.000342)	[11]
Transition probability hyperglycaemia to target glycaemia	0.999072 (0.000928)	0.999339 (0.000661)	[11]
Transition probability hyperglycaemia to hypoglycaemia[a]	0.000016 (0.000016)	0.0000312 (0.0000312)	[11]
Transition probability hyperglycaemia to hyperglycaemia[a]	0.000546 (0.000546)	0.000269 (0.000269)	[11]
Transition probability hyperglycaemia to in-hospital death[a]	0.000366 (0.000366)	0.000360 (0.000360)	[11]
Number of POCT glucose per day	4.84 (3.07)	8.01 (4.48)	Time and motion study
Number of days on ICU	5.60 (2.60)	5.60 (2.60)	[11]
Number of days mechanical ventilation	3.23 (7.60)	3.23 (7.60)	[11]
Number of days dialysis treatment	0.49 (2.80)	0.49 (2.80)	[11]
Number of days on general ward	11.73 (8.13)	11.73 (8.13)	[11]
Number of red blood cell transfusions per patient	1.79 (0.11)	1.93 (0.10)	[20]
Number of platelet transfusions per patient	0.13 (0.02)	0.15 (0.01)	[20]
Number of plasma transfusions per patient	0.52 (0.06)	0.54 (0.04)	[20]
Number of Cofact administrations per patient	0.06 (0.01)	0.02 (0.01)	[21]
Time per glucose measurement (min)	3.10 (0.89)	3.10 (0.89)	Time and motion study
Period of write off Accu-Chek® Inform II	5 years (NA)	5 years (NA)	Roche manual

ICU intensive care unit, *NA* not applicable, *POCT* point-of-care test, *SE* standard error, *SGC* strict glycaemic control

[a] Because of the limited availability of data on the occurrence of hyper- and hypoglycaemic events and in-hospital death, the SE of these transitions was conservatively set to be equal to the mean probability of this transition

Nearly all BG measurements (97 %) were performed at the bedside using BG-POCT devices (Accu-Chek® Inform; Roche, Almere, The Netherlands), but BG could be measured in the central laboratory when the BG-POCT devices were not functioning due to calibration issues. Less than 5 % of BG measurements were performed on a blood gas analyser. Therefore, those were not considered in this analysis.

All patients in the model started in the 'target glycaemia' state. In each 30-min cycle of the simulation, patients might remain in the 'target glycaemia' state defined as a BG level of 4.4–6.1 mmol/L or transition to either a 'hypoglycaemia' state, defined as a BG level <4.4 mmol/L, or a 'hyperglycaemia' state, defined as a BG level >6.1 mmol/L (and vice versa), or to the 'in-hospital death' state (absorbing state) (Fig. 1). This cycle length was applied because the data showed that it is long enough to (on average) capture one transition per cycle and short enough to have not more than one transition occurring per cycle. Cohort age was matched to the study sample, which is 65 years. Patient transitions are tracked from the start of ICU admission onwards until hospital discharge. The model was face-validated by clinical (MJS, PES, RTMvH) and health economic (LMGS, HM, MMAK) experts.

2.2 Outcome Parameters

The primary effectiveness measure was a BG level within the target of the SGC guideline (i.e. 4.4–6.1 mmol/L) [13]. Based on the model, the expected differences in cost and effects of the SGC guideline compared to the situation pre-SGC guideline implementation is evaluated and presented as the incremental cost-effectiveness ratio (ICER). The 95 % confidence interval (CI) around the ICER is calculated using Fieller's theorem [16]. The secondary effectiveness measure is in-hospital mortality.

Table 2 Cost parameters used in the model

Variable	Costs [€] (SE)	References
POCT instrument purchased	1693.00 (169.30)	Roche diagnostics
Maintenance contract per instrument per year	56.00 (5.60)	Roche diagnostics
POCT measurement	1.56 (0.16)	Roche diagnostics, and average multicentre data time and motion study
Labour and medication time of hypo- or hyperglycaemic event	6.40 (0.64)	[19] and assumption
ICU day	2183.00 (1021.86)	Average multicentre data
Mechanical ventilation day	400.00 (940.48)	Average multicentre data
Dialysis day	283.56 (1613.59)	Average multicentre data
General ward day	630.20 (436.69)	[20]
Red blood cell transfusion	220.30 (22.03)	[20]
Platelet transfusion	531.56 (53.16)	[20]
Plasma transfusion	189.61 (18.96)	[20]
Cofact infusion	183.95 (18.40)	[21]

ICU intensive care unit, *POCT* point-of-care test, *SE* standard error

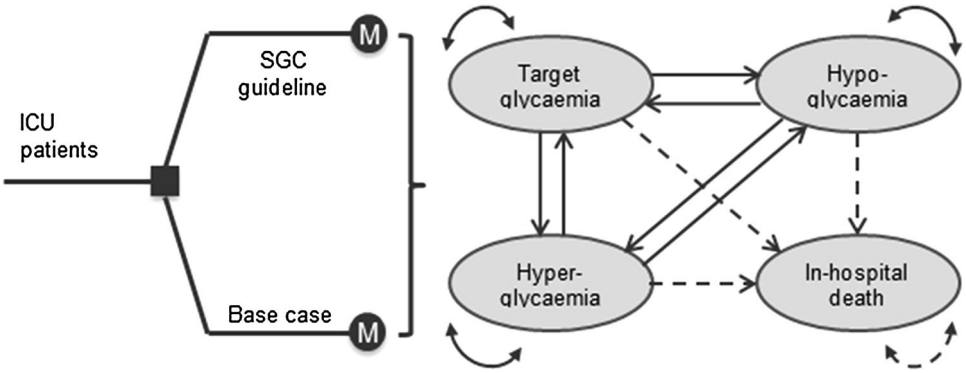

Fig. 1 Cost-effectiveness model structure. Within each 30-min cycle of the model, patients can transition to each of the four health states. 'In-hospital death' represents the absorbing state. *ICU* intensive care unit, *SGC* strict glycaemic control

2.3 Transition Probabilities

Transition probabilities between the different health states, for each 30-min cycle of the model, were derived from the dataset of the original publication [11]. For each hospitalisation episode, only the first ICU admittance/stay was considered. The first POC glucose measurement following ICU admission was excluded from the analysis to avoid issues with BG levels that cannot be influenced by the SGC guideline.

2.4 Resource Use

The average daily number of POC glucose measurements was 4.8 before, compared with 8.0 after, guideline implementation [11]. Nurse time involved in performing a POC glucose analysis was based on a 3-day observation period in each of the participating hospitals. It was assumed that 99 % of the time per measurement was spent by nurses and only 1 % by physicians.

The additional time required to treat patients with either hypoglycaemia or hyperglycaemia, was estimated to involve 5 min nurse labour time and 1 min medical doctor labour time. The length of stay, on the general ward and the ICU, mechanical ventilation and dialysis treatment were not significantly different before and after implementation of the guideline in both groups [11]. Therefore, data from pre-SGC guideline implementation served as input for those four parameters in the model. The in-hospital death rate was corrected for the age-dependent background mortality rates [17].

2.5 Costs Included in the Model

All unit costs are based on public sources and are presented in Table 2. Costs of disposables used for POC glucose measurements were based on expert estimations obtained in the three participating hospitals. Unit costs of 1 day of ICU stay, mechanical ventilation and dialysis treatment

Table 3 Summary of cost-effectiveness results

Parameter	Pre-SGC guideline [mean (95 % CI)]	SGC guideline [mean (95 % CI)]	Incremental effect SGC guideline vs. pre-SGC guideline [mean (95 % CI)]
Number of patients in target glucose level	881 (588–1339)	895 (597–1360)	14 (9–21)
Total direct hospital costs per patient per year (€)	20,617 (13,775–31,337)	20,972 (14,012–31,877)	355 (237–539)
Incremental cost per patient in target glucose level (ICER) (€)			25 (−31 to 38)

CI confidence interval, *ICER* incremental cost-effectiveness ratio, *SGC* strict glycaemic control

were estimated based on both administrative data of a Dutch academic hospital as well as from the tariffs published by the Dutch Healthcare Authority (NZa) [18]. Costs of POC tests (including the maintenance contract, write-off period of the POC instrument, disposables and test strips used, as well as the costs of labour time) were converted to costs per 30-min cycle of the model. Total costs were calculated by multiplying resource use with the accompanying unit prices. All costs have been converted to price year 2013 using Dutch consumer price index levels and are presented in euros [19–22].

2.6 Sensitivity Analyses

To test the robustness of the model outcomes against changes in the input parameters, all input parameters were subjected to one-way sensitivity analyses. Results of the sensitivity analyses are reported by means of tornado diagram, indicating the impact of a change in parameter value on the resulting ICER. Because in the pre-SGC guideline implementation situation no difference between hospital days, mechanical ventilation and dialysis days is assumed, the sensitivity analysis evaluates the effect of imputing the non-statistical differences that have been reported in the dataset by Schultz et al. [11].

3 Results

The implementation of an SGC guideline was associated with an increase in the number of BG-POCT from an average of 4.8 (95 % CI 2.6–6.7) to 8.0 (95 % CI 4.1–11.2) per patient per day. This involves an increase of mean BG-POCT costs from €8.57 to €13.56 per patient (+58 %) in the SGC protocol versus the situation before implementation of the guideline. When taking total hospital costs and clinical effects into account, implementation of the SGC guideline increased total expected mean hospital costs during inpatient stay from €20,617 to €20,972, an expected mean increase of €355 (95 % CI 237–539) per patient. Besides increased costs of BG-POCT, the remaining increase in costs is mainly attributable to the costs of the POCT analyser and of blood products. On the effectiveness side, the number of patients in target glucose levels increased by 14 (95 % CI 9–21) patients per 1000, indicating an increase of 1.4 % (from 881 to 895). This translates to an incremental cost-effectiveness ratio (ICER) of €25 (95 % CI –31 to 38) per additional patient within the target glucose level (Table 3). When combining this with the average length of hospitalisation episode of 17.3 days (which corresponds to 830 model cycles), the SGC guideline is expected to increase the number of cycles (i.e. time) that patients are in target glucose from 88.1 % of cycles (i.e. 731 per 830) before implementation to 89.5 % (i.e. 743 per 830) after implementation of the SGC guideline. This indicates an increase of 5.5 h, or 11 cycles, in target glucose per patient per hospitalisation episode. For a Dutch hospital with approximately 500 ICU patients per year, this would indicate an increase in costs of €177,310 per year and an increase of 119 days (i.e. 5706 cycles) that patients will be in their target glucose during their hospitalisation episode.

Concerning the secondary effectiveness measure, the results of this study show no significant change in overall hospital mortality despite a higher incidence of hypoglycaemia [11]. Notably, a statistically significant decrease in hospital mortality among patients with one or more episodes of severe hypoglycaemia from 47.5 % before implementation of the SGC guidelines to 29.5 % after is observed. This corresponds with an ICER of €19.70 per 1 % reduction in hospital mortality for patients with severe hypoglycaemic episode(s). The parameters that most strongly influence the expected cost effectiveness are summarised in a tornado diagram (Fig. 2). The net change in the duration of ICU stay has the largest impact on the incremental cost effectiveness of the SGC guideline. Other parameters that considerably affect the cost effectiveness of SGC are its impact on the duration of stay on a general ward, and the costs per POC glucose test. An overview of all results from the sensitivity analyses is provided in the Appendix; outcomes are per patient.

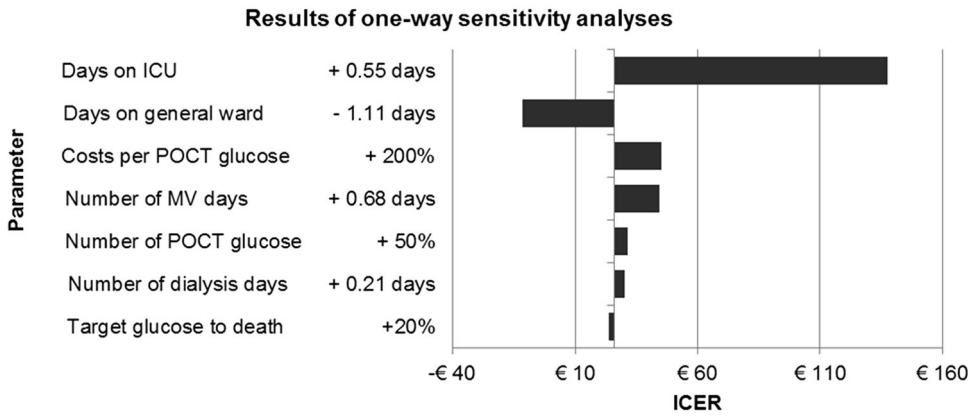

Fig. 2 Tornado diagram showing the effect of changes in model input parameters on the incremental cost-effectiveness ratio, which is expressed as the incremental costs per additional patient in the target glucose level. *ICER* incremental cost-effectiveness ratio, *ICU* intensive care unit, *MV* mechanical ventilation, *POCT* point-of-care test

4 Discussion

Implementation of a guideline to achieve strict glycaemic control in ICU patients using frequent glucose POC testing is expected to lead to an increase of 1.4 % (i.e. 14 per 1000) of patients in target glucose control per 30-min cycle, and a patient would spend on average 5.5 h more (i.e. 11 additional cycles) in their target glycaemic state during hospitalisation. Although the incidence of severe hypoglycaemia was found to be higher after implementation of this guideline, in-hospital mortality rates in those patients decreased by 18 %. Improved overall control of glycaemic status of patients or its potential consequences comes at an increase in BG-POCT costs of €4.99 (+58 %) per patient, but total cost increase of only 1.8 % (€355) per patient. This clearly illustrated why costs of POCT should not be considered in isolation, because they actually affect the costs and effectiveness of the entire inpatient episode of care. While the current analysis assumes that the SGC guideline will not affect overall hospital length of stay, a study by Van den Berghe et al. [23] reported that SGC in mechanically ventilated ICU patients resulted in a reduction in ICU length of stay, lower incidence of blood transfusions and lower mechanical ventilation dependency. This was associated with substantial cost savings compared with conventional insulin therapy [23].

Besides the increase in the number of BG-POCT measurements, the additional costs reported in the current study are attributable to the higher incidence of hypoglycaemia observed after implementation of the SGC guideline, as its treatment accrues additional costs. However, as suggested in the study by Schultz et al. [11], the incidence of severe hypoglycaemia might decrease over time as a result of a learning effect among the nurses. If so, the costs of executing the SGC guideline will likely decrease over time, along with the expected decrease in hypoglycaemic events. The cost effectiveness of implementation of the SGC guideline was most sensitive to variations in the duration of ICU stay and days on a general ward.

The current study has several strengths and weaknesses that should be acknowledged. The main strength of this analysis is that it is the first to estimate the total opportunity costs of an SGC guideline, taking both the costs of POCT glucose into account as well as the downstream costs, and to relate this to the effectiveness of treatment (defined as the number of patients in target glucose levels). A limitation in every health economic analysis is that assumptions need to be made where empirical data are unavailable or non-existent. The assumptions made for this analysis pertain to the amount of time that both a doctor and a nurse spend on treating a patient with either hypo- or hyperglycaemia, and the costs of accompanying glucose or insulin administration. Concerning the estimation of the costs of this insulin or glucose administration, no specific data could be obtained from the literature. However, costs of insulin are known to be about €0.03 per International Unit. In addition, the average amount of glucose or insulin that was administered was difficult to determine. Since this may vary strongly between patients, costs per insulin or glucose administration to treat either a hypo- or hyperglycaemic event were conservatively estimated to be €2.00 per patient per event.

Further, the current analysis was performed in a multisite setting in The Netherlands. While this makes the results generalisable to the Dutch context, transferring them to other countries or settings requires adaptation of the model inputs to reflect local costs and practice variations. For example, in the current study, ICU nurses already practiced POC BG control prior to implementation of the SGC guideline, which may not be the case in other countries. Also, implementation of the SGC guideline requires the availability of a laboratory information system, which may not be commonly available in different countries. Therefore, those additional costs should be taken into account when informing decisions concerning

implementation of this guideline in other countries. Finally, while most pharmacoeconomic guidelines, including the Dutch one [20], recommend a societal perspective on costs and effects, with a preference for expressing outcomes in quality-adjusted life-years, this study adopted a hospital perspective and chose clinical outcome measures that better resonated the actual decision context for the intervention under study.

5 Conclusion

Implementation of the SGC guideline likely increases the number and time that patients are in target glucose control during their hospitalisation episode, at a relatively small increase in total costs.

Conflict of interest The implementation study, previously published by Schultz et al. 2012, was supported by a grant from the Netherlands Organization for Health Research and Development [11]. The health economic model development was supported by a grant from Roche Diagnostics International Ltd. (represented by Ms. Mulder), of which Monteban Value Services (represented by Ms. Monteban) and PANAXEA (represented by Ms. Kip and Dr. Steuten) were the beneficiaries. All other authors have no conflicts of interest to declare.

Author contributions Authors van Hooijdonk, Steuten, Kip, Monteban, Mulder, Spronk and Schultz made substantial contributions to the conception and planning of the work that led to the manuscript and to the acquisition, analysis and interpretation of data. Authors van Braam Houckgeest, van der Sluijs and Abu-Hanna made substantial contributions to the conception and planning of the work that led to the manuscript and to the interpretation of data. Authors van Hooijdonk, Steuten, Kip and Monteban drafted the paper and critically revised the manuscript for important intellectual content. Authors Mulder, Spronk, Schultz, van Braam Houckgeest, van der Sluijs and Abu-Hanna critically revised the manuscript for important intellectual content. All authors approved the final submitted version of the paper. Dr. Steuten is guarantor for the overall content.

Appendix

See Table 4.

Table 4 Results of one-way sensitivity analysis

Type	Parameter	Base-case difference	Change in difference	ICER (cost per patient in target glucose) (€)	Difference in discounted costs (€)	Differencein discounted effect
Base case				25	355	14
Transition probabilities	Target glucose to hypoglycaemia	+0.000070	+5 %	25.80	354.69	13.75
			+10 %	25.81	354.76	13.75
			+15 %	25.82	354.83	13.74
			+20 %	25.83	354.90	13.74
	Hypoglycaemia to hypoglycaemia	+0.000068	+5 %	25.78	354.62	13.75
			+10 %	25.78	354.62	13.75
			+15 %	25.78	354.62	13.75
			+20 %	25.78	354.62	13.75
	Hyperglycaemia to hypoglycaemia	+0.000016	+5 %	25.78	354.62	13.75
			+10 %	25.78	354.62	13.75
			+15 %	25.78	354.62	13.75
			+20 %	25.78	354.62	13.75
	Target glucose to hyperglycaemia	–0.000017	+5 %	25.78	354.62	13.75
			+10 %	25.78	354.61	13.75
			+15 %	25.78	354.61	13.76
			+20 %	25.78	354.60	13.76
	Hypoglycaemia to hyperglycaemia	+0.000016	+5 %	25.78	354.62	13.75
			+10 %	25.78	354.62	13.75
			+15 %	25.78	354.62	13.75
			+20 %	25.78	354.62	13.75
	Hyperglycaemia to hyperglycaemia	–0.000277	+5 %	25.78	354.62	13.75
			+10 %	25.78	354.62	13.75
			+15 %	25.78	354.62	13.75
			+20 %	25.78	354.62	13.75

Table 4 continued

Type	Parameter	Base-case difference	Change in difference	ICER (cost per patient in target glucose) (€)	Difference in discounted costs (€)	Differencein discounted effect
	Target glucose to death	–0.000039	+5 %	25.25	364.86	14.45
			+10 %	24.76	375.11	15.15
			+15 %	24.32	385.37	15.85
			+20 %	23.91	395.64	16.55
	Hypoglycaemia to death	–0.000046	+5 %	25.78	354.62	13.75
			+10 %	25.78	354.62	13.75
			+15 %	25.78	354.62	13.75
			+20 %	25.78	354.63	13.75
	Hyperglycaemia to death	–0.000006	+5 %	25.78	354.62	13.75
			+10 %	25.78	354.62	13.75
			+15 %	25.78	354.62	13.75
			+20 %	25.78	354.62	13.75
Hospital stay	ICU days	0.00	+0.55 days	137.53	1457.76	10.60
	General ward days	0.00	–1.11 days	–11.41	–228.13	19.99
	MV days	0.00	+0.68 days	44.29	609.13	13.75
	CVVH days	0.00	+0.21 days	30.05	413.23	13.75
POCT	Measurements per day	3.20	+50 %	31.30	430.44	13.75
	Costs per measurement		+100 %	37.31	513.19	13.75
			+200 %	48.84	671.77	13.75

CVVH continuous venous haemofiltration (dialysis), *ICER* incremental cost-effectiveness ratio, *ICU* intensive care unit, *MV* mechanical ventilation, *POCT* point-of-care test

References

1. Price CP. Point of care testing. BMJ. 2001;322(7297):1285–8.
2. Lee-Lewandrowski E, Lewandrowski K. Perspectives on cost and outcomes for point-of-care testing. Clin Lab Med. 2009;29(3):479–89.
3. Finfer S, Wernerman J, Preiser JC, et al. Clinical review: consensus recommendations on measurement of blood glucose and reporting glycemic control in critically ill adults. Crit Care. 2013;17(3):229.
4. Schultz MJ, Harmsen RE, Spronk PE. Clinical review: strict or loose glycemic control in critically ill patients–implementing best available evidence from randomized controlled trials. Crit Care. 2010;14(3):223.
5. Schultz MJ, Spronk PE, van Braam Houckgeest F. Glucontrol, no control, or out of control? [letter]. Intensive Care Med. 2010;36(1):173–4 **(author reply 175–6)**.
6. Vriesendorp TM, DeVries JH, van Santen S, et al. Evaluation of short-term consequences of hypoglycemia in an intensive care unit. Crit Care Med. 2006;34(11):2714–8.
7. Krinsley J, Schultz MJ, Spronk PE, et al. Mild hypoglycemia is strongly associated with increased intensive care unit length of stay. Ann Intensive Care. 2011;1:49.
8. Krinsley JS, Schultz MJ, Spronk PE, et al. Mild hypoglycemia is independently associated with increased mortality in the critically ill. Crit Care. 2011;15(4):R173.
9. Egi M, Bellomo R, Stachowski E, et al. Hypoglycemia and outcome in critically ill patients. Mayo Clin Proc. 2010;85(3):217–24.
10. Nice-Sugar Study Investigators, Finfer S, Chittock DR, et al. Intensive versus conventional glucose control in critically ill patients. N Engl J Med. 2009;360(13):1283–97.
11. Schultz MJ, Harmsen RE, Korevaar JC, et al. Adoption and implementation of the original strict glycemic control guideline is feasible and safe in adult critically ill patients. Minerva Anestesiol. 2012;78(9):982–95.
12. Dellinger RP, Carlet JM, Masur H, Surviving Sepsis Campaign Management Guidelines Committee, et al. Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. Crit Care Med. 2004;32(3):858–73.
13. van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. N Engl J Med. 2001;345(19):1359–67.
14. Van den Berghe G, Wilmer A, Hermans G, et al. Intensive insulin therapy in the medical ICU. N Engl J Med. 2006;354(5):449–61.
15. Van den Berghe G, Wilmer A, Milants I, et al. Intensive insulin therapy in mixed medical/surgical intensive care units: benefit versus harm. Diabetes. 2006;55(11):3151–9.
16. Willan AR, O'Brien BJ. Confidence intervals for cost-effectiveness ratios: an application of Fieller's theorem. Health Econ. 1996;5(4):297–305.
17. Central Bureau of Statistics (NL). Levensverwachting in 2012 vrijwel onveranderd. 2013. http://www.cbs.nl/nl-NL/menu/themas/bevolking/publicaties/artikelen/archief/2013/2013-3786-wm.htm. Accessed 30 June 2013
18. Nederlandse Zorgautoriteit, Bijlage 1 bij tariefbeschikking TB/CU-7041-03. 2013. http://www.nza.nl/1048076/1048155/Bijlage_bij_TB_CU_7041_03_Tarieflijst_eerstelijnsdiagnostiek.pdf. Accessed 1 July 2013

19. Tan SS, Hakkaart-van Roijen L, Al MJ, et al. A microcosting study of intensive care unit stay in the Netherlands. J Intensive Care Med. 2008;23(4):250–7.
20. Hakkaart-van Roijen L, Tan SS, Bouwmans CAM. Handleiding voor kostenonderzoek; Methoden en standaard kostprijzen voor economische evaluaties in de gezondheidszorg. Rotterdam: Institute for Medical Technology Assessment, Erasmus University Rotterdam; 2010. p. 1–127.
21. Sanquin Bloedvoorziening, Prijslijst 2013, Prijzen en leveringsvoorwaarden. Sanquin Blood Supply, Amsterdam; 2013. p. 1–16.
22. Centraal Bureau voor de Statistiek. Consumentenprijzen; prijsindex 2006 = 100. 2015. http://statline.cbs.nl/StatWeb/publication/?DM=SLNL&PA=71311NED&D1=0&D2=0&D3=64,77,90,103,116,129,142,155,168,181,194,219,232,245&VW=T. Accessed 5 Feb 2014.
23. Van den Berghe G, Wouters PJ, Kesteloot K, et al. Analysis of healthcare resource utilization with intensive insulin therapy in critically ill patients. Crit Care Med. 2006;34(3):612–6.