



Strict blood glucose control with insulin during intensive care after cardiac surgery: impact on 4-years survival, dependency on medical care, and quality-of-life

Catherine Ingels, Yves Debaveye, Ilse Milants, Erik Buelens, Ann Peeraer, Yves Devriendt, Tom Vanhoutte, Aurelie Van Damme, Miet Schetz, Pieter J. Wouters, and Greet Van den Berghe

Department of Intensive Care Medicine, University Hospital Gasthuisberg, Catholic University of Leuven, B-3000 Leuven, Belgium

Received 24 November 2005; revised 3 March 2006; accepted 9 March 2006; online publish-ahead-of-print 11 April 2006

KEYWORDS

Cardiac surgery;
Intensive care;
Critical care;
Glycaemia;
Insulin;
Survival;
Quality-of-life

Aims To document the impact of intensive insulin therapy during intensive care on long-term (4 years) outcome of high-risk cardiac surgery patients.

Methods and results In this pre-planned sub-analysis and follow-up study of a large, randomized controlled trial on the effects of intensive insulin therapy during critical illness, we assessed long-term outcome in the 970 patients who had been admitted after high-risk cardiac surgery (mean \pm SD EuroSCORE of 6.0 ± 3.7 ; EuroSCORE-predicted hospital mortality of 9.9%; observed hospital mortality of 7.5% in the conventional insulin group and 3.4% in the intensive insulin group). Long-term outcome was quantified as: (a) 4 years survival; (b) incidence of hospital re-admission; (c) level of activity and medical care requirements at 4 years as assessed by the Karnofsky score; and (d) perceived health-related quality-of-life at 4 years as assessed by the Nottingham Health Profile. Four years after ICU admission, the number of post-hospital discharge deaths was similar in the two study groups, reflecting maintenance of the acute survival benefit with intensive insulin therapy. Survivors who had been treated with intensive insulin during ICU stay revealed a similar risk for hospital re-admission and a comparable level of dependency on medical care. There was no effect on quality-of-life in the total group, whereas the increased survival of sicker patients with at least 3 days of insulin therapy evoked a more compromised perceived quality-of-life, in particular regarding social and family life.

Conclusion The short-term survival benefit obtained with insulin-titrated glycaemic control during intensive care after cardiac surgery was maintained after 4 years, without inducing increased medical care requirements but possibly at the expense of compromised perceived quality of social and family life.

Introduction

Intensive insulin therapy during intensive care has shown to improve intensive care and in-hospital survival and to reduce morbidity of critically ill patients in a surgical intensive care unit (ICU).¹ In-hospital mortality was significantly reduced from 11 to 7% in the entire group of surgical patients. In the subgroup of long-stay patients, however, the benefit was much more pronounced with mortality reduced from 21 to 14% in patients treated for at least 3 days and from 26 to 17% in patients treated for at least 5 days. A large fraction of the patients in this study were admitted to ICU after cardiac surgery. Survival of this subgroup, most of them not known with a diagnosis of diabetes, also improved in line with a previous observational study in

patients with diabetes mellitus,² but details of how intensive insulin therapy affected this predominantly non-diabetic patient population have not yet been reported.

Assessing long-term outcome is important to confirm a sustained impact of an intervention that proved to exert an acute beneficial outcome effect during hospitalization. Long-term outcome can be defined as number of deaths after an extended time period, but also hospital re-admission and the need for medical care. Investigating risk of hospital re-admission and the level of activity and medical care requirements is important, as any intervention, by improving short-term survival and returning sicker patients into society, may increase the burden on the patient, his/her relatives, and on society. According to the WHO, health is not only the absence of disease or infirmity, but also the presence of physical, mental, and social well-being.³ Two recent literature reviews on quality-of-life

*Corresponding author. Tel: +32 16 34 40 21; fax: +32 16 34 40 15.
E-mail address: greta.vandenbergh@med.kuleuven.be

after critical illness conclude that intensive care survivors have a lower quality-of-life when compared with the general population.^{4,5} Hence, health-related quality-of-life is also an important post-intensive care long-term outcome variable. Although it is difficult to assess, it is important to consider when allocating resources and evaluating the effects of new treatments.

In the current study of the subgroup of patients included in the original insulin study after cardiac surgery, we also studied long-term outcome, 4 years after patients had been admitted to ICU. We quantified this long-term outcome as: (a) 4 years survival; (b) incidence of hospital re-admission during those 4 years; (c) level of activity and medical care requirements at 4 years; and (d) perceived health-related quality-of-life at 4 years.

Methods

This study is a pre-planned sub-analysis ($n = 970$) and follow-up of the cardiac surgery patients who had been included in a large ($n = 1548$), prospective, randomized controlled trial on the effects of intensive insulin therapy on outcome of critical illness.¹ The detailed protocol of the study and the characteristics of the patients have been previously published.¹ The study complies with the declaration of Helsinki. The original study and the current long-term follow-up protocol were approved by the Institutional Ethical review board and informed consent was obtained from all patients, their legal guardians, and/or their family doctors or the referring specialists.

In the original study, all mechanically ventilated, adult patients admitted to our surgical ICU had been eligible for inclusion. After stratification for reason of ICU admission, patients had been randomized to either strict blood glucose control below 6.1 mmol/L (110 mg/dL) with intensive insulin therapy, or to the conventional approach which only recommended insulin therapy when blood glucose levels exceeded 12 mmol/L (220 mg/dL). We here report the data from the subgroup of 970 patients admitted after cardiac surgery, either electively or after secondary complications. As previous observational studies have indicated that insulin therapy requires at least 3 days in order to exert potential benefit in this patient population,⁶ we planned to also assess this subgroup of long-stay patients.

Outcome measures

Primary endpoint for the current study was 4-years all cause mortality and the number of post-hospital discharge deaths. Secondary endpoints were 2- and 3-years survival, hospital re-admission during the 4 years following ICU admission, the level of activity and medical care requirements assessed by the Karnofsky Performance Status Scale at 4 years⁷ and the perceived quality-of-life assessed by a validated Dutch translation of the Nottingham Health Profile (NHP) at 4 years.⁸

The Karnofsky Performance Scale⁷ was originally designed to determine the objective activity level of patients older than 17 years. The scale ranges from 0% (dead) to 100% (normal activity, no complaints, no evidence of disease). A score of 60% is an important threshold as patients scoring 60% or higher are able to take care of most of their own needs, requiring only occasional or no assistance.

Quality-of-life refers to the physical, psychological, and social aspects of a subject's well-being and is influenced by various factors such as personal experiences, beliefs, expectations, and perceptions.^{9–11} The NHP was developed and validated by Hunt *et al.*¹² as a simple tool to detect perceived health-related problems. The NHP consists of a standardized questionnaire divided into two parts.

The first one is composed of statements related to six dimensions: physical mobility, energy, pain, sleep, social isolation, and emotional

reactions. The patients respond to these statements with yes or no, according to whether or not the statement applies to them 'in general'. For each positive answer a weighted score is given. The higher the score, the more limitations or distress are being experienced by the patient. The maximum score on any section is 100.

The second part consists of seven questions referring to those domains of daily life most often affected by health: paid employment, tasks around the home, social life, family relationships, sex life, hobbies and interests, and holidays. The patient answers to these questions with yes or no when his actual health-status influences or does not influence each of the seven fields. The higher the score, the greater the problems perceived in those areas.

The NHP has been used previously to assess the health-related quality-of-life in critically ill patients after heart transplantation,¹³ coronary artery bypass grafting,¹⁴ cardiac surgery,¹⁵ and trauma.¹⁶ For the current study, carried out in Dutch-speaking Belgium, we used the validated Dutch version of the NHP.⁸

The patients or their next of kin were contacted by phone. If either of these were unavailable, we contacted their family doctors or the referring specialists. Some data could be collected from the hospital database. When we could not reach any of the above, we checked at the civil registration service of the patient's hometown, whether he or she was still alive, or if there had been a change in domicile.

As we previously reported for the total study population, we here also report the detailed impact of strict blood glucose control with intensive insulin therapy on ICU morbidity, ICU mortality, and in-hospital mortality in the studied subset of cardiac surgery patients. The ICU morbidity measures included time to weaning from mechanical ventilation, days in ICU, newly acquired acute renal failure requiring dialysis or continuous veno-venous haemofiltration, incidence of hyperbilirubinaemia (>2 mg/dL), electromyographical evidence of critical illness polyneuropathy assessed by weekly EMG, need for red-cell transfusions, hyperinflammation as indicated by the highest level of C-reactive protein which is measured daily, and cumulative TISS-28 score as a quantitative index of invasive therapy over time in ICU.

Statistical analysis

Normally distributed data are presented as means \pm SD and skewed data as medians and inter-quartile range (IQR), unless indicated otherwise.

The effect of intensive insulin therapy on the time course of long-term mortality was assessed by Kaplan–Meier analysis (Mantel–Cox log-rank test). The effect of intensive insulin therapy on the time course of weaning from mechanical ventilation, ICU discharge, and hospital discharge was analysed by cumulative hazard and Mantel–Cox log-rank testing, censoring for early deaths. Other differences between study groups were analysed by χ^2 test, unpaired Student's *t*-test, and Mann–Whitney-*U* test, when appropriate. A two-sided *P*-value of 0.05 was considered significant.

Results

Patient characteristics at baseline

Patients after cardiac surgery randomized to receive conventional or intensive insulin therapy during intensive care were comparable at baseline for gender, age, BMI, type of cardiac surgery, EuroSCORE (www.euroscore.org), first 24 h APACHE II¹⁷ and TISS-28¹⁸ score, history of malignancy, and diabetes (Table 1). The EuroSCORE-predicted mortality was 9.9% in this high-risk patient cohort with an observed mortality of 5.5%. In the total group of 970 cardiac surgery patients, blood glucose level upon ICU admission was slightly higher in the conventional group when compared with the intensive insulin group, a difference that was no longer

Table 1 Baseline patient characteristics

	All 970 patients		250 patients in ICU for ≥ 3 days	
	Conventional	Intensive	Conventional	Intensive
Insulin treatment				
<i>n</i>	493	477	136	114
Male gender (total number, %)	361 (73)	330 (69)	93 (68)	69 (61)
Age (years) (mean \pm SD)	65 \pm 11	66 \pm 11	67 \pm 11	68 \pm 10
BMI (kg/m ²) (mean \pm SD)	26.5 \pm 4.5	26.8 \pm 4.6	26.5 \pm 5.9	26.8 \pm 4.6
EuroSCORE (mean \pm SD)	6.1 \pm 3.7	5.8 \pm 3.6	8.0 \pm 4.1	7.6 \pm 4.3
Predicted mortality based on EuroSCORE (%, mean \pm SD)	10.5 \pm 13.6	9.2 \pm 12.8	17.0 \pm 17.4	15.2 \pm 18.1
Type of cardiac surgery (total number, %)				
Isolated coronary surgery	260 (53)	285 (60)	64 (47)	61 (54)
Isolated valve repair	138 (28)	106 (22)	30 (22)	23 (20)
Corrections cong anomalies, combined surgery or transplant surgery	95 (19)	86 (18)	42 (31)	30 (26)
First 24 h APACHE II score (median and IQR)	9 (7–12)	9 (6–12)	11 (8–14)	10 (7–13)
First 24 h TISS score (median and IQR)	45 (42–47)	44 (42–47)	46 (43–48)	46 (44–48)
History of malignancy (total number, %)	17 (3.4)	17 (3.6)	6 (4.4)	2 (1.8)
History of diabetes (total number, %)				
Insulin treated	24 (4.9)	27 (5.7)	8 (5.9)	8 (7.0)
Oral anti-diabetic treatment and/or diet	59 (11.9)	47 (9.9)	17 (12.5)	13 (11.4)
On admission blood glucose (mmol/L) (mean \pm SD)	7.9 \pm 2.8	7.4 \pm 2.3	8.7 \pm 3.7	8.0 \pm 2.9

APACHE-II score: Acute Physiology and Chronic Health-II score; IQR: interquartile range; TISS: Therapeutic intervention scoring system.

present in the subset of patients requiring at least a third day of intensive care.

Insulin therapy and blood glucose control

Virtually all patients in the intensive insulin group required insulin in order to maintain blood glucose levels at the set target (Table 2). The insulin dose was also higher and the blood glucose level significantly lower in the intensive insulin group, conform the study protocol. Fourteen patients in the intensive insulin group (2.9%) and 2 patients in the conventional group (0.4%) experienced an episode of hypoglycaemia (blood glucose level ≤ 40 mg/dL or 2.2 mmol/L, $P = 0.002$).

Effect of intensive insulin therapy on ICU morbidity and mortality and in-hospital mortality

As reported previously for all ICU patients, intensive insulin therapy also reduced ICU and in-hospital mortality of patients admitted after high-risk cardiac surgery (Table 3). This was true for all 970 patients and for the subset of patients in ICU for at least a third day. In addition, morbidity was reduced, most pronounced in the group of patients in ICU for at least a third day, as indicated by earlier weaning from mechanical ventilation, shorter ICU stay, less acute renal failure, reduced incidence of critical illness polyneuropathy, fewer patients requiring red cell transfusions, reduced inflammation, and lowered cumulative TISS-28 score (Table 4, Figure 1). In contrast to the total group, the effect on blood stream infections in ICU was not significant. Also the cumulative chance for hospital discharge over time was enhanced with intensive insulin therapy, censored for early deaths (Figure 1).

Table 2 Insulin therapy and blood glucose control

	Conventional	Intensive	<i>P</i> -value
Received insulin therapy (no., %)			
All	193 (39.1)	470 (98.5)	<0.0001
In ICU for at least a third day	82 (60.3)	113 (99.1%)	<0.0001
Mean daily insulin dose (IU per day) (median, IQR)			
All	0 (0–11)	55 (37–78)	<0.0001
In ICU for at least a third day	3 (0–28)	66 (45–100)	<0.0001
Mean morning blood glucose (mmol/L) (mean \pm SD)			
All	8.7 \pm 3.6	5.8 \pm 1.0	<0.0001
In ICU for at least a third day	8.9 \pm 1.6	5.8 \pm 0.7	<0.0001
Days on insulin infusion (median, IQR)			
All	0 (0–1)	2 (2–3)	<0.0001
In ICU for at least a third day	2 (0–4)	6 (4–8)	<0.0001

The patients who left the hospital alive were mostly discharged to their homes. The number of patients who needed to be transferred to another hospital, long-term care facility, or to rehabilitation homes was higher in the intensive insulin group (59 patients, 12.8%) than in the conventional group (27 patients, 5.9%) ($P = 0.0004$). For the patients in ICU at least a third day, this was 14 patients

Table 3 Mortality analysis

Variable	Conventional	Intensive	P-value
Deaths during intensive care (no., %)	25/493 (5.1)	10/477 (2.1)	0.01
Among patients receiving intensive care for at least a third day (no., %)	21/136 (15.4)	7/114 (6.1)	0.02
Causes of death in ICU (no., %)			0.03
Multiple organ failure with proven septic focus	8 (32)	0 (0)	
Multiple organ failure, no detectable septic focus	7 (28)	2 (20)	
Severe brain damage	3 (12)	0 (0)	
Acute cardiovascular collapse	7 (28)	8 (80)	
In-hospital deaths (no., %)	37/493 (7.5)	16/477 (3.4)	0.005
Among patients receiving intensive care for at least a third day (no./total no., %)	30/136 (22.1)	9/114 (7.9)	0.002
Long-term mortality (2 years after ICU admission) (no., %) (<i>n</i> = 941)	56/477 (11.7)	32/464 (6.9)	0.01
Among patients receiving intensive care for at least a third day (no./total no., %) (<i>n</i> = 199)	38/130 (29.2)	11/108 (10.2)	0.0003
Long-term mortality (3 years after ICU admission) (no., %) (<i>n</i> = 941)	66/477 (13.8)	50/464 (10.8)	0.1
Among patients receiving intensive care for at least a third day (no./total no., %) (<i>n</i> = 199)	40/130 (30.8)	16/108 (14.8)	0.004
Long-term mortality (4 years after ICU admission) (no., %) (<i>n</i> = 941)	89 (18.7)	73 (15.7)	0.2
Among patients receiving intensive care for at least a third day (no./total no., %) (<i>n</i> = 199)	47 (36.1)	25 (23.1)	0.03

(13.3%) in intensive group vs. 7 patients (6.6%) in the conventional group ($P = 0.1$).

Effect of intensive insulin therapy on long-term (4 years) mortality

Data were available for 941 (97%) patients, 477 in the conventional group and 464 in the intensive group. At 4 years, 18.7% of the patients in the conventional group had died vs. 15.7% in the intensive group ($P = 0.2$) (Table 3). This number included a post-hospital discharge mortality rate after 4 years of 12.7% in the conventional group and 12.0% in the intensive insulin group ($P = 0.8$). For the long-stay patients, at 4 years, 36.2% of patients in the conventional insulin group had died vs. 23.1% in the intensive group ($P = 0.03$), including a post-hospital discharge mortality rate after 4 years of 18.0% in the conventional insulin group and 16.2% in the intensive group ($P = 0.7$).

At 2 years, 11.7% of the patients in the conventional group had died vs. 6.9% in the intensive group ($P = 0.01$). For the long-stay patients, this was 29.2 vs. 10.2%, respectively ($P = 0.0003$). At 3 years, 13.8% of the patients in the conventional group had died vs. 10.8% in the intensive group ($P = 0.1$). For the long-stay patients, this was 30.8 vs. 14.8%, respectively ($P = 0.004$).

The impact of intensive insulin therapy during ICU stay on the time course of mortality over 4 years is shown in Figure 2.

The cause of late, post-hospital discharge mortality was identifiable for 98 patients, 48 in the conventional group and 50 in the intensive group. There was no difference between

the two insulin groups for these causes of late death ($P = 0.3$), with the most prevalent cause of late mortality being cardiovascular disease (39%), followed by malignancy (23%), and subsequently neurological complications (8%).

Effect of intensive insulin therapy on level of activity and medical care requirements 4 years post-ICU admission

During the 4 years following cardiac surgery, 131 in the conventional group (27.5%) and 133 hospital survivors of the intensive group (28.7%) required a hospital re-admission for any reason ($P = 0.7$). Among the patients treated in ICU for at least a third day, this was 29 patients in the conventional group (22.3%) vs. 32 patients in the intensive insulin group (29.6%) ($P = 0.2$).

Data on the Karnofsky score were available for 753 (78%) patients, 372 in the conventional group and for 381 in the intensive group. Four years after cardiac surgery, in the total group of cardiac surgery patients, there was no significant difference in the median level of Karnofsky score between patients in the conventional or intensive insulin groups (Table 5). However, patients who received at least 3 days intensive insulin therapy had a significantly higher Karnofsky score (median 70 vs. 60%, $P = 0.04$) when compared with patients treated conventionally. This was mainly attributable to the higher survival rate in the intensive insulin group, as there was no difference between the two groups when considering survivors only, the median Karnofsky score being 80% in both groups. More than 80% of the studied patients reached a Karnofsky score of

Table 4 ICU morbidity analysis

Variable	Conventional (n = 493)	Intensive (n = 477)	P-value
Extubated within 48 h after surgery (no., %)	380 (77)	395 (83)	0.026
Duration of ventilatory support (no. of days, median and IQR)			
All	1 (1-2)	1 (1-2)	0.1
In ICU for at least a third day	5 (3-13)	4 (2-6)	0.004
Duration of intensive care (no. of days, median and IQR)			
All	2 (2-4)	2 (2-3)	0.4
In ICU for at least a third day	7 (5-15)	6 (4-8)	0.004
Dialysis or continuous veno-venous haemofiltration (no., %)			
All	28 (5.7)	10 (2.1)	0.004
In ICU for at least a third day	27 (19.9)	9 (7.9)	0.007
Hyperbilirubinaemia (peak bilirubin >2 mg/dL) (no., %)			
All	108 (21.9)	75 (15.7)	0.01
In ICU for at least a third day	64 (47.1)	41 (35.9)	0.07
Bloodstream infection (no., %)			
All	12 (2.4)	9 (1.9)	0.6
In ICU for at least a third day	12 (8.8)	9 (7.9)	0.8
Electromyographic evidence of critical-illness polyneuropathy (no./total no., %)			
All	34 (6.9)	9 (1.9)	0.0002
In ICU for at least a third day	34 (25.0)	9 (7.9)	0.0004
Red cell transfusions			
All	109 (22.1)	84 (17.6)	0.07
In ICU for at least a third day	80 (58.8)	52 (45.6)	0.04
Highest level of C-reactive protein (mg/L) (median and IQR)			
All	188 (125-246)	185 (141-230)	0.9
In ICU for at least a third day	249 (205-296)	216 (173-260)	0.002
Cumulative TISS-28 (median and IQR)			
All	89 (74-150)	88 (76-132)	0.3
In ICU for at least a third day	279 (172-575)	224 (162-314)	0.002

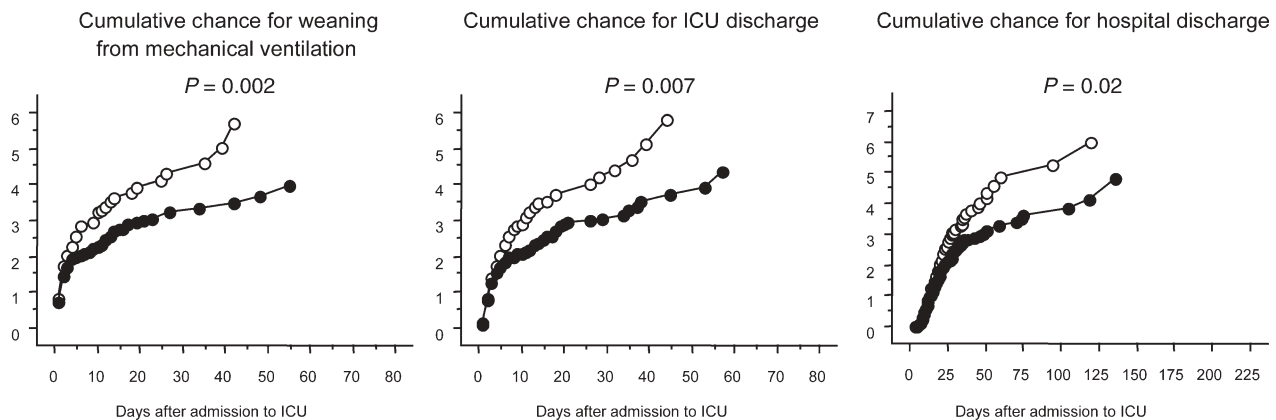


Figure 1 Effect of intensive insulin therapy of all 970 cardiac surgery patients on time on mechanical ventilation, time in ICU, and time in the hospital. Filled circles depict conventionally treated patients and open circles the intensive insulin treated patients. P-values were obtained by log-rank (Mantel-Cox) significance testing and were censored for early deaths.

≥60%, indicating an acceptable level of autonomy, 4 years after discharge from intensive care for cardiac surgery.

Effect of intensive insulin therapy on quality-of-life 4 years after ICU admission

For part I of the NHP, data were only available for 603 (62%) patients, 303 in the conventional group and 300 patients

in the intensive group. For part II of the questionnaire, only 403 (42%) patients provided an answer, 197 in the conventional group and 205 patients in the intensive group.

For the first part of the NHP (Table 6, upper part), there was no significant difference between the conventional and the intensive insulin treatment groups. The dimensions mostly affected by prolonged critical illness were 'sleep' and 'physical mobility'.

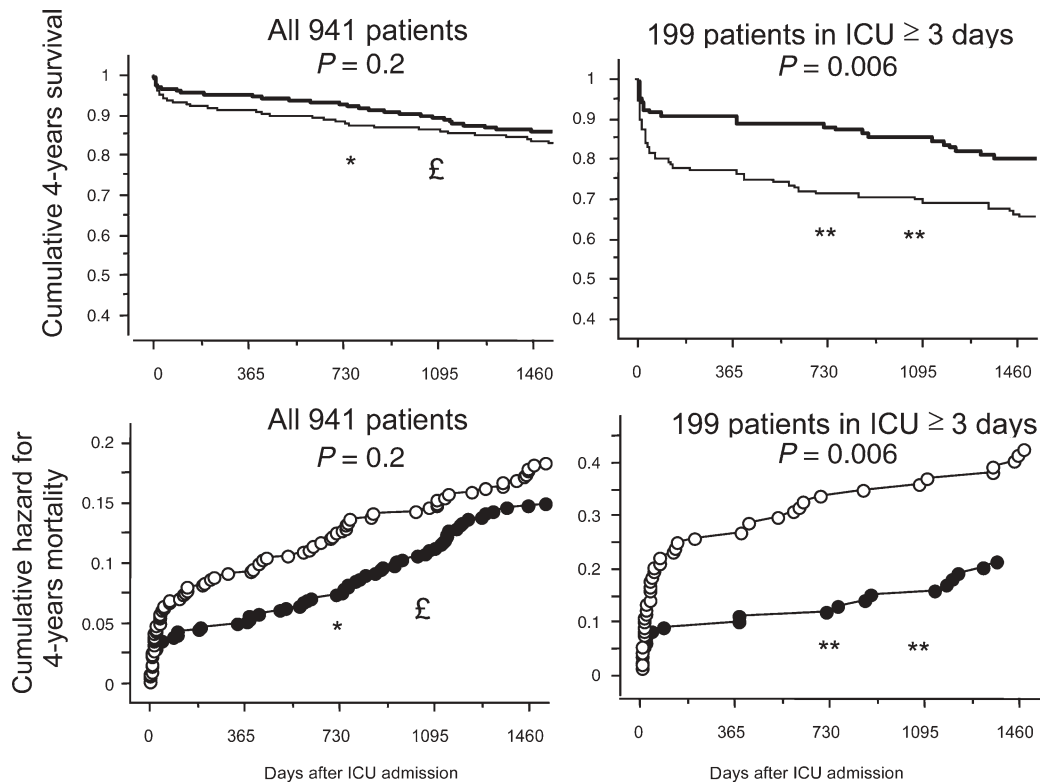


Figure 2 Kaplan-Meier survival curves and cumulative hazard plots of the time course of mortality from inclusion in the study until 4 years later, of all 941 patients who had been admitted to ICU after cardiac surgery and of those 199 patients who required at least a third day of intensive care and of whom long-term follow-up data were available. Thick lines and filled circles represent patients in the intensive insulin group and thin lines and open circles the patients in the conventional insulin group. *P*-values were obtained by log-rank Mantel-Cox test. The symbols indicate levels of significance after 2 and 3 years, respectively. £*P* = 0.1; **P* < 0.05; ***P* < 0.01.

Table 5 Karnofsky Performance Status Scale

	Conventional (<i>n</i> = 372)	Intensive (<i>n</i> = 381)	<i>P</i> -value
Karnofsky % (survivors and non-survivors) (median, IQR)			
All	80 (50-90)	80 (60-90)	0.9
In ICU for at least a third day	60 (0-80)	70 (0-90)	0.04
Karnofsky % (survivors only) (median, IQR)			
All	80 (70-90)	80 (70-90)	0.4
In ICU for at least a third day	80 (70-90)	80 (70-90)	0.4
Karnofsky ≥ 60% (no., %)			
All	308 (86.0)	297 (82.3)	0.2
In ICU for at least a third day	58 (78.4)	57 (80.3)	0.8

The second part of the NHP (Table 6, upper part), consists of seven aspects of life mostly affected by health status. Only for the prolonged critically ill patients, who had been in ICU for at least 3 days, there was a significant difference between the conventional and the intensive treatment group, with higher (worse) scores in the dimensions concerning household activities, social life, and family life (Table 6).

Discussion

We assessed the long-term outcome of 941 of the 970 patients after cardiac surgery, who had been included in a large randomized controlled trial on the effect of strict blood glucose control with insulin during ICU stay, 4 years after admission to intensive care. The post-hospital discharge mortality was similar in the two groups. Of the patients who had been treated at least a third day with intensive insulin during intensive care, more survived the 4-years post-ICU episode than those who were treated conventionally. Although, more in-hospital survivors from the intensive insulin group had been initially discharged to another hospital, long-term facilities, or rehabilitation homes, at 4-years follow-up, patients who had been treated with intensive insulin during ICU stay revealed a comparable level of dependency on medical care. The increased survival of sicker long-ICU stay patients evoked a more compromised perceived quality-of-life, in particular regarding social and family life. This indicated that short-term glycaemic control with insulin during intensive care after cardiac surgery clearly evoked long-term survival benefits without inducing an increase in medical care requirements but at the expense of a moderately compromised perceived quality-of-social and family life.

As reported previously for the mixed population in surgical intensive care,¹ strict blood glucose control during ICU stay also reduced intensive care and in-hospital mortality among the subset of high-risk cardiac surgery patients, which was

Table 6 Nottingham Health Profile

	Conventional	Intensive	P-value
<i>NHP I</i>	<i>n</i> = 303	<i>n</i> = 300	
Emotional responses (median, IQR)			
All	0 (0-9)	0 (0-9)	0.5
In ICU for at least a third day	0 (0-17)	0 (0-15)	0.8
Pain (median, IQR)			
All	0 (0-8)	0 (0-8)	0.6
In ICU for at least a third day	0 (0-16)	0 (0-8)	0.7
Energy (median, IQR)			
All	0 (0-3)	0 (0-3)	0.4
In ICU for at least a third day	0 (0-6)	0 (0-6)	0.9
Sleep (median, IQR)			
All	0 (0-10)	0 (0-10)	0.9
In ICU for at least a third day	5 (0-15)	5 (0-10)	0.6
Social isolation (median, IQR)			
All	0 (0-0)	0 (0-0)	0.7
In ICU for at least a third day	0 (0-0)	0 (0-0)	0.6
Physical mobility (median, IQR)			
All	0 (0-16)	0 (0-16)	0.5
In ICU for at least a third day	8 (0-24)	8 (0-24)	0.6
Sum of all scores (median, IQR)			
All	13 (0-45)	15 (0-48)	0.4
In ICU for at least a third day	26 (8-73)	30 (0-66)	0.6
<i>NHP II</i>	<i>n</i> = 197	<i>n</i> = 205	
Current health condition has an impact on ability to work (no., %)			
All	24 (12.2)	21 (10.5)	0.6
In ICU for at least a third day	5 (12.2)	6 (14.3)	0.8
Current health condition has an impact on household activities (no., %)			
All	85 (43.3)	93 (46.3)	0.6
In ICU for at least a third day	21 (51.2)	31 (73.8)	0.03
Current health condition has an impact on social life (no., %)			
All	67 (34.2)	83 (41.3)	0.1
In ICU for at least a third day	17 (41.5)	27 (64.3)	0.04
Current health condition has an impact on family life (no., %)			
All	35 (17.9)	51 (25.4)	0.07
In ICU for at least a third day	8 (19.5)	16 (38.1)	0.06
Current health condition has an impact on sexual activity (no., %)			
All	57 (29.1)	58 (28.9)	>0.9
In ICU for at least a third day	14 (34.1)	16 (38.1)	0.7
Current health condition has an impact on interest and hobbies (no., %)			
All	60 (30.6)	74 (36.8)	0.2
In ICU for at least a third day	15 (36.6)	22 (52.4)	0.1
Current health condition has an impact on holidays (no., %)			
All	56 (28.6)	64 (32.0)	0.5
In ICU for at least a third day	13 (31.7)	17 (40.5)	0.4
Sum of all scores (median, IQR)			
All	0 (0-2)	0 (0-3)	0.4
In ICU for at least a third day	1 (0-3)	1 (0-4)	0.6

most pronounced among those patients treated for at least a third day. The reason why ICU death was prevented in this population was not cardiovascular, but rather prevention of failure of other organ systems with or without sepsis. Also the effects in morbidity, previously reported for the entire study population, such as prevention of prolonged dependency on mechanical ventilation, organ failure,

transfusion requirement, and prevention of excessive inflammation, were present in this subset of high-risk cardiac surgery patients, again most pronounced in the group of patients that received at least a few days treatment. Potential mechanisms of action include protection of neurons,¹⁹ the endothelium,²⁰ and of hepatocyte mitochondrial ultrastructure and function.²¹ Risk of

hypoglycaemia appeared smaller in this cardiac surgery cohort than in the total surgical ICU study population, which could be explained by a larger fraction of patients who only need a short time in ICU.

The clinical benefit of the short-term therapy, when given for at least a third day in intensive care, was preserved after discharge from hospital, as reflected by lower 4-year mortality rate in the intensive insulin group. The most prevalent causes of death during the 4 years following hospital discharge were cardiovascular disease, malignancies, and neurological complications.

More patients who had been treated by intensive insulin during the time in ICU, survived the initial hospitalization. As expected, because lives were saved, more of these survivors in the intensive insulin group were sicker at the time of discharge from our University hospital and needed to be transferred to another hospital, long-term facilities, or rehabilitation homes. At 4-years follow-up, however, a similar proportion of these initially sicker patients were still alive. Furthermore, they also revealed a comparable level of dependency on medical care than the patients surviving conventional therapy (who were initially less sick) as assessed by (a) incidence of re-admission to hospital for whatever reason and (b) the Karnofsky score. This indicates that rehabilitation of the initial survivors from the intensive insulin group was as good as normal. The increased survival of sicker prolonged critically ill (those in ICU for ≥ 3 days) cardiac patients evoked a more compromised perceived quality-of-life, in particular regarding social and family life. Indeed, higher, and thus worse, scores were noted in this subgroup for these aspects. Although these data indicate that there may have been a certain trade-off, a compromise on quality-of-life, for the better survival with intensive insulin therapy, the impact is fairly limited. From a socio-economic viewpoint, this is an important finding.

Some limitations of our study need to be highlighted. First limitation of this study it that it was performed in a single centre and it was not feasible to achieve strict blinding because safe insulin titration requires blood glucose monitoring. This may have induced bias particularly in the assessment of ventilation weaning and ICU discharge. However, at 4 years follow-up, the patients, the physicians, the next of kin, and the investigators performing the questionnaires were unaware of insulin treatment allocation. Secondly, as we did not perform a baseline (before cardiac surgery) analysis of the Karnofsky score or the NHP questionnaire, we could not assess the impact of the surgery and intensive care as such on these endpoints. Finally, incomplete data on the Karnofsky and NHP (only assessed when the patient could be interviewed and was willing to discuss the at times personal items) results may have caused bias.

In conclusion, 4 years after admission to intensive care, the improved short-term outcome of cardiac surgery patients with intensive insulin therapy, particularly of those who were in ICU for at least a third day, was maintained as more patients were still alive when compared with those who had received conventional insulin therapy. Survivors who had been treated with intensive insulin during ICU stay revealed a comparable level of dependency on medical care. These benefits came at the expense of a moderately compromised perceived quality of social and

family life for prolonged critically ill patients. Short-term glycaemic control with insulin during intensive care thus clearly evoked sustained outcome benefits, particularly for prolonged critically ill cardiac surgery patients, without inducing a substantial burden for the patient, his/her relatives, or society.

Acknowledgements

The authors wish to thank Ellen Vleminckx for data entering; the ICU clinical fellows for severity of illness scoring; and the ICU nurses for daily TISS scoring and excellent protocol compliance. Supported by Research grants from the Belgian Fund for Scientific Research (G.0278.03 to GVdB), the Research Council of the University of Leuven (OT/03/56 to GVdB), the Belgian Foundation for Research in Congenital Heart Diseases (GVdB), and an unrestricted research grant from Novo Nordisk, Denmark (GVdB). This article was guest edited by Prof. Lars Ryden, Karolinska Hospital, Stockholm, Sweden.

Conflict of interest: G.V.D.B., via the Catholic University of Leuven, received a non-restrictive research grant from Novo Nordisk Denmark.

References

1. Van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyincx F, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P, Bouillon R. Intensive insulin therapy in critically ill patients. *N Engl J Med* 2001;345:1359-1367.
2. Furnary AP, Gao G, Grunkemeier GL, Wu Y, Zerr KJ, Bookin SO, Floten S, Starr A. Continuous insulin infusion reduces mortality in patients with diabetes undergoing coronary artery bypass grafting. *J Thorac Cardiovasc Surg* 2003;125:1007-1021.
3. Constitution of the World Health Organization. *Handbook of Basic Documents*. 5th ed. Palais des Nations, Geneva: World Health Organization; 1952. p3-20.
4. Dowdy D, Eid M, Sedrakyan A, Mendez-Tellez P, Pronovost P, Herridge M, Needham D. Quality of life in adult survivors of critical illness: a systematic review of the literature. *Intens Care Med* 2005;31:611-620.
5. Hennessy D, Kelsey J, Yergens D, Noseworthy T, Doig C. Outcomes of elderly survivors of intensive care. A review of the literature. *Chest* 2005;127:1764-1774.
6. Garber A, Moghissi E, Bransome E, Clark N, Clement S, Cobin R, Furnary A, Hirsch I, Levy P, Roberts R, Van den Berghe G, Zamudio V. American College of Endocrinology Task Force on inpatient diabetes metabolic control. *Endocr Pract* 2004;10:77-82.
7. Yates JW, Chalmer B, McKeegney FP. Evaluation of patients with advanced cancer using the Karnofsky performance status. *Cancer* 1980;45:2220-2224.
8. Erdman R, Passchier J. The Dutch version of the Nottingham Health Profile: investigation and psychometric aspects. *Psychol Rep* 1993;72:1027-1035.
9. Brook R, Ware J, Davies-Avery A, Stewart A, Donald C, Rogers W. *Conceptualizations and Measurements of Health for Adults in the Health Insurance Study*. Vol. VIII, overview. Santa Monica, CA: Rand Corporation; 1979.
10. Patrick D, Bush J, Chen M. Toward an operational definition of health. *J Health Soc Behav* 1973;14:6-23.
11. Brook RH, Ware JE, Rogers WH, Keeler EB, Davies AR, Donald CA, Goldberg GA, Lohr KN, Masthay PC, Newhouse JP. Does free care improve adult's health? Results from a randomized controlled trial. *N Engl J Med* 1983;309:1426-1434.
12. Hunt S, McEwen J, McKenna S. Measuring health status: a new tool for clinicians and epidemiologists. *J Roy Coll Gen Pract* 1985;35:185-188.
13. O'Brien BJ, Banner NR, Gibson S, Yacoub MH. The Nottingham Health Profile as a measure of quality of life following heart and lung transplantation. *J Epidemiol Commun Health* 1987;42:232-234.
14. Caine N, Harrison SC, Sharples LD, Wallwork J. Prospective study of quality of life before and after coronary artery bypass grafting. *BMJ* 1991;302:511-516.

15. Nielsen D, Sellgren J, Ricksten S-E. Quality of life after cardiac surgery complicated by multiple organ failure. *Crit Care Med* 1997;52:195-202.
16. Thiagarajan J, Taylor P, Hogbin E, Ridley S. Quality of life after multiple trauma requiring intensive care. *Anaesthesia* 1994;49:211-218.
17. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med* 1985;13:818-829.
18. Miranda DR, de Rijk A, Schauffeli W. Simplified Therapeutic Intervention Scoring System: the TISS-28 items—results from a multicentre study. *Crit Care Med* 1996;24:64-73.
19. Van den Berghe G, Schoonheydt K, Beex P, Bruyninckx F, Wouters P. Insulin therapy protects the central and peripheral nervous system of intensive care patients. *Neurology* 2005;64:1348-1353.
20. Langouche L, Vanhorebeek I, Vlasselaers D, Vander Perre S, Wouters P, Skogstrand K, Hansen T, Van den Berghe G. Intensive insulin therapy protects the endothelium of critically ill patients. *J Clin Invest* 2005;115:2277-2286.
21. Vanhorebeek I, De Vos R, Mesotten M, Wouters PJ, De Wolf-Peeters C, Van den Berghe G. Protection of hepatocyte mitochondrial ultrastructure and function by strict blood glucose control with insulin in critically ill patients. *Lancet* 2005;365:53-59.

Clinical vignette

doi:10.1093/eurheartj/ehi895

Online publish-ahead-of-print 27 April 2006

Patent foramen ovale with a riding vermicular thrombus causing paradoxical and massive pulmonary embolism

Dirk Sibbing^{1*}, Matthias Overbeck², Roland Schmidt¹, Jochen Gaa³, and Petra Barthel¹

¹Department of Cardiology, Deutsches Herzzentrum München & 1. Medizinische Klinik, Technische Universität München, Munich, Germany; ²Department of Cardiac Surgery, Deutsches Herzzentrum München, Munich, Germany; ³Department of Radiology, Klinikum rechts der Isar, Technische Universität München, Munich, Germany

*Corresponding author. E-mail address: dirk@sibbing.net

A 46-year-old adipose woman was admitted to hospital with tachycardia and progressive dyspnoea. The week before hospitalization she collapsed several times and two days before admission she experienced an intermittent motorical weakness of her right hand. Transthoracic echocardiography revealed decreased right ventricular (RV) function, RV dilatation, and signs of pulmonary hypertension with a pressure gradient of 43 mmHg across the tricuspid valve. A patent foramen ovale was found with a mobile continuous structure in both atria spanning through the foramen and prolapsing over both tricuspid and mitral valve in diastole (Movie 1). Computed tomography (CT) scan showed massive bilateral pulmonary embolism (Panel A) due to deep vein thrombosis of the lower extremity and a structure in both atria with the appearance of a thrombus (Panel B). Transesophageal echocardiography clearly visualized a biatrial vermicular thrombus (Panel C, Movie 2). Cranial magnetic resonance imaging showed multiple bihemispheric hyperintense signal spots using fluid-attenuated inversion recovery presumably due to paradoxical intracerebral embolism. Intravenous heparin treatment was initiated and the patient was admitted to the cardiac surgery department. Biatrial and pulmonary thrombectomy was undertaken (Panels D and E). The post-operative course was uneventful with a substantial drop in transvalvular pressure to 21 mmHg 13 days after surgery. Oral anticoagulation was initiated and the patient recovered completely. This clinical case is an impressive example of pulmonary embolism subsequently causing pulmonary hypertension and paradoxical embolism via a patent foramen ovale.

See online supplementary material for Movies 1 and 2 available at *European Heart Journal* online.

Panel A. Axial multislice CT image of massive bilateral pulmonary embolism (see arrows).

Panel B. Axial multislice CT image of the atrial structure consistent with thrombus (see arrow). RA, right atrium; LA, left atrium.

Panel C. Transesophageal echocardiographic image in the oblique plane (62°), at the level of the aortic root. A vermicular thrombus is trapped in a patent foramen ovale. RA, right atrium; LA, left atrium; PFO, patent foramen ovale; Ao, aorta.

Panel D. Intraoperative view with the vermicular thrombus (see arrow) in the right atrium. RV, right ventricle; RA, right atrium.

Panel E. Thrombus after operative removal. The asterisk (*) denotes the area where the thrombus was trapped in the patent foramen ovale. RA, right atrium; LA, left atrium.

Movie 1. Zoomed section from a transthoracic four-chamber view showing a large, very mobile thrombus crossing from the right to the left atrium via a patent foramen ovale. Both ends of the thrombus are prolapsing through the AV valves into the right and left ventricles.

Movie 2. Transesophageal echocardiographic view in the oblique plane (62°) at the level of the aortic root showing a vermicular, very mobile thrombus stacking in a patent foramen ovale and reaching from the right atrium to the left atrium.

