

Tight Blood Glucose Control Is Renoprotective in Critically Ill Patients

Miet Schetz, Ilse Vanhorebeek, Pieter J. Wouters, Alexander Wilmer, and Greet Van den Berghe

Department of Intensive Care Medicine, Catholic University of Leuven, Leuven, Belgium

ABSTRACT

Two large, prospective, randomized, controlled trials have shown a beneficial effect of intensive insulin therapy (IIT) on the kidney function of critically ill patients. The data from these trials were combined for performance of a more detailed analysis of the renoprotective effect of IIT. After exclusion of 41 patients with preadmission ESRD, the study sample comprised 2707 critically ill patients who were randomly assigned to conventional or IIT. A modified risk-injury-failure-loss-ESRD (mRIFLE) system was used to classify acute kidney injury such that mRIFLE-Injury and -Failure (mR-IF) corresponded to peak serum creatinine levels $\geq 2\times$ and $\geq 3\times$ the admission levels, respectively. IIT significantly reduced the incidence of mR-I or -F from 7.6 to 4.5% ($P = 0.0006$), and this renoprotective effect was most pronounced in patients who achieved strict normoglycemia. In surgical patients, IIT also significantly reduced oliguria (from 5.6 to 2.6%; $P = 0.004$) and the need for renal replacement therapy (from 7.4 to 4.0%; $P = 0.008$). In medical patients, the incidence of mR-I or -F decreased to a lesser extent, perhaps because a greater severity of illness at admission may have rendered preventive therapies less effective. In conclusion, this secondary analysis of two large, randomized, controlled trials suggests that IIT, with a goal of achieving normoglycemia, protects the renal function of critically ill patients.

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Depending on the definition and case mix, acute kidney injury (AKI) affects 4 to 25% of intensive care unit (ICU) patients with mortality rates that mostly exceed 40%.¹ Evidence exists that not only overt acute renal failure but also mild increases in serum creatinine are independently associated with mortality.^{2–6} Prevention of AKI therefore remains an important target in critical care medicine. Besides maintaining adequate hemodynamics and avoiding nephrotoxic substances, no pharmaceutical agents have conclusively been demonstrated to protect the kidney of ICU patients.^{7,8}

Several large clinical trials have shown that strict blood glucose control in both type 1 and type 2 diabetes has a beneficial effect on the development and progression of diabetic nephropathy (reviewed by Fioretto *et al.*⁹). In addition, diabetes is a generally recognized risk factor for AKI in several settings.¹⁰ Hyperglycemia and insulin resistance are also common in critically ill patients, even in those

without diabetes,^{11,12} and are associated with increased morbidity and mortality.^{13–19} Observational trials, after correction for diabetes and other known risk factors, have shown an association between pre- or intraoperative hyperglycemia and postoperative AKI after cardiac surgery,^{20,21} between hyperglycemia at cardiac catheterization and contrast nephropathy,²² and between hyperglycemia during total parenteral nutrition and the development of AKI.²³ Whether the degree of hyperglycemia simply reflects the severity of illness or is

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Correspondence: Dr. Miet Schetz, Department of Intensive Care Medicine, University Hospital Gasthuisberg, University of Leuven, 3000 Leuven, Belgium. Phone: 32-16-344021; Fax: 32-16-344015; E-mail: marie.schetz@uz.kuleuven.ac.be

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actually contributing to the adverse renal outcome can be demonstrated only by a randomized trial comparing correction or tolerance of the elevated blood glucose levels.

Two such trials were recently performed. A first randomized, controlled trial (RCT) in 1548 predominantly surgical ICU patients showed that strict blood glucose control with intensive insulin treatment (IIT) not only reduced ICU and hospital mortality but also decreased the incidence of AKI in critically ill surgical patients.²⁴ A second large RCT that had a similar design and was performed in the medical ICU of the same center also demonstrated a protective effect on the kidney.²⁵ The beneficial renal effect of IIT was further confirmed by a large observational study in a medical-surgical ICU.²⁶

We here report a more detailed analysis of the effect of IIT on renal function in the study populations of the two RCT. In addition, we explore potential mechanisms explaining this

renoprotective effect in the subset of surgical patients with prolonged ICU stay.

RESULTS

Clinical Renal Outcome among All 2707 Patients

The baseline characteristics of the patients were comparable at randomization (Table 1). The renal outcome data and associated mortality are presented in Table 2. Approximately 20% of all patients developed one of the adverse renal outcomes, and every adverse renal outcome was significantly associated with an increased mortality. A total of 149 (53%) of the oliguric patients and 147 (51%) of all patients who required RRT did not meet our modified risk-injury-failure-loss-ESRD (mRIFLE) criteria because they already had an increased se-

Table 1. Baseline patient characteristics in the whole study population ($n = 2707$); Comparison between conventional insulin treatment and IIT and between medical and surgical patients^a

Parameter	Conventional ($n = 1366$)	Intensive ($n = 1341$)	<i>P</i>	Surgical ($n = 1540$)	Medical ($n = 1167$)	<i>P</i>
Age (mean \pm SD)	62.8 \pm 14.8	63.3 \pm 14.7	0.41	62.8 \pm 13.8	63.4 \pm 15.9	0.27
Male gender (n [%])	926 (67.9)	886 (66.1)	0.31	1094 (71.0)	719 (61.6)	<0.0001
Body mass index (median [IQR])	24.7 (22.3 to 27.7)	24.9 (22.8 to 28.2)	0.02	25.7 (23.0 to 28.7)	24.2 (22.0 to 27.3)	<0.0001
Creatinine upon admission (mg/dl; median [IQR])	1.11 (0.86 to 1.51)	1.08 (0.86 to 1.50)	0.27	1.07 (0.89 to 1.33)	1.18 (0.83 to 1.95)	<0.0001
Creatinine >2.5 mg/dl upon admission (n [%])	130 (9.7)	129 (9.4)	0.82	61 (4)	198 (17)	<0.0001
Bilirubin upon admission (mg/dl; median [IQR])	0.91 (0.53 to 1.65)	0.88 (0.56 to 1.52)	0.49	0.92 (0.64 to 1.44)	0.80 (0.43 to 1.96)	0.0002
Bilirubin >2 mg/dl upon admission (n [%])	217 (18.1)	239 (19.6)	0.34	180 (14.0)	276 (24.4)	<0.0001
CRP level upon admission (mg/L; median [IQR])	89 (42 to 184)	90.1 (43 to 190)	0.64	77 (48 to 139)	109 (37 to 219)	<0.0001
Blood glucose upon admission (mg/dl; median [IQR])	135 (109 to 170)	138 (112 to 176)	0.06	131 (107 to 162)	147 (116 to 189)	<0.0001
Hyperglycemia \geq 200 mg/dl upon admission (n [%])	222 (16.3)	194 (14.5)	0.19	173 (11.2)	244 (20.9)	<0.0001
History of diabetes (n [%])	195 (14.3)	201 (14.9)	0.61	204 (13.2)	194 (16.6)	0.014
History of malignancy (n [%])	238 (17.4)	252 (18.8)	0.36	239 (15.5)	251 (21.5)	<0.0001
APACHE II score on admission (median [IQR])	13 (8 to 22)	13 (8 to 20)	0.41	9 (7 to 13)	22 (17 to 29)	<0.0001
Diagnostic category (n [%])			0.99			<0.0001
Cardiovascular disease/cardiac or vascular surgery	546 (40.0)	527 (39.3)		1028 (66.7)	48 (4.1)	
Respiratory disease/thoracic surgery	316 (23.2)	315 (23.5)		121 (7.9)	510 (43.7)	
Gastrointestinal or hepatic disease/major abdominal surgery	207 (15.2)	199 (14.8)		103 (6.9)	303 (26.0)	
Neurology/neurosurgery	60 (4.4)	63 (4.7)		62 (4.0)	60 (5.1)	
Renal/metabolic	21 (1.5)	27 (2.0)		0 (0.0)	48 (4.1)	
Hematology/oncology	50 (3.7)	44 (3.3)		0 (0.0)	94 (8.1)	
Solid organ transplant	44 (3.2)	46 (3.4)		90 (5.8)	0 (0.0)	
Polytrauma	34 (2.5)	33 (2.5)		68 (4.4)	0 (0.0)	
Other	86 (6.3)	87 (6.5)		68 (4.4)	0 (0.0)	

^aIQR, interquartile range.

Table 2. Incidence and mortality of the different renal outcome categories and comparison between medical and surgical patients

Outcome Parameter	n (%)	Surgical/Medical (%); OR (95% CI)	P ^a	Mortality (%) Yes/No; OR (95% CI)	P ^b	Surgical/Medical; OR (95% CI)	P ^c
mR-R	163 (6.4)	4.8/8.5; 1.83 (1.33 to 2.52)	0.0002	46/17; 4.21 (3.04 to 5.83)	<0.0001	25/62; 4.80 (2.43 to 9.47)	<0.0001
mR-I	101 (3.8)	3.2/4.7; 1.50 (1.01 to 2.24)	0.0460	63/19; 7.51 (4.95 to 11.40)	<0.0001	58/68; 1.51 (0.67 to 3.41)	0.3200
mR-F	63 (2.3)	1.8/3.1; 1.78 (1.08 to 2.96)	0.0200	71/20; 9.74 (5.59 to 16.97)	<0.0001	63/78; 2.06 (0.68 to 6.24)	0.2000
mR-IF	164 (6.1)	4.9/7.6; 1.61 (1.17 to 2.22)	0.0030	66/19; 8.60 (6.13 to 12.08)	<0.0001	60/72; 1.71 (0.89 to 3.28)	0.1100
Oliguria	283 (10.5)	4.2/18.0; 5.33 (3.99 to 7.12)	<0.0001	76/15; 17.20 (12.80 to 23.00)	<0.0001	67/78; 1.74 (0.94 to 3.21)	0.0800
Need for RRT	291 (10.7)	5.7/17.4; 3.48 (2.67 to 4.52)	<0.0001	66/16; 10.20 (7.80 to 13.30)	<0.0001	58/70; 1.69 (1.01 to 2.84)	0.0470
AKI	516 (19.4)	11.9/28.5; 2.96 (2.42 to 3.62)	<0.0001	60/13; 10.50 (8.40 to 13.00)	<0.0001	44/69; 2.88 (1.98 to 4.18)	<0.0001

^aP for the difference in incidence between medical and surgical patients and for the respective OR.

^bP for the difference in mortality according to the presence or absence of the renal outcome category and the respective OR.

^cP for the difference in mortality between medical and surgical patients with the respective renal outcome and the respective OR.

rum creatinine upon admission (2.2 mg/dl [1.4 to 3.6] and 2.4 mg/dl [1.5 to 3.6], respectively), reflecting acute and/or chronic kidney disease. Compared with the surgical patients, the incidence of all adverse renal outcomes was significantly higher in the medical patients. Being admitted to the medical ICU increased the risk for development mRIFLE-Injury and -Failure (mR-IF) with odds ratio (OR) of 1.62 (95% confidence interval [CI] 1.17 to 2.22; $P = 0.003$). Of the 98 hospital survivors who required RRT during their ICU stay, 11% remained dialysis dependent at hospital discharge.

The renal outcome data in the IIT and conventional treatment groups are shown in Table 3. IIT reduced the incidence of mR-I from 4.6 to 3.0% ($P = 0.03$) and mR-F from 3.1 to 1.5% ($P = 0.004$). As reported in the original publications, the incidence of mR-IF decreased from 7.6 to 4.5% ($P = 0.0006$). There was no significant effect on the mildest category of mR-R or on the incidence of oliguria or need for RRT. Renal recovery occurred in 44 (92%) of 48 hospital survivors with strict blood glucose control and in 43 (86%) of 50 of those with conventional therapy ($P = 0.4$).

The renoprotective effect of IIT seemed to be most pronounced in the surgical group, in which the protection by IIT was also significantly present for oliguria (2.6 versus 5.6%; $P = 0.003$), the need for RRT (4.0 versus 7.4%; $P = 0.003$), and the combined end point of AKI (10.0 versus 13.7%; $P = 0.03$). In the medical patients only, the incidence of mR-IF was significantly reduced by IIT (6 versus 9.2%; $P = 0.04$; Figure 1, Table 3).

Compared with surgical patients, medical patients were

more severely ill upon ICU admission, as indicated by a higher APACHE II score; higher admission serum creatinine; and more patients with admission bilirubin >2 mg/dl, admission hyperglycemia >200 mg/dl, and history of diabetes or malignancy (Table 1). This is also reflected by a higher hospital mortality (38 versus 9%; $P < 0.0001$). Forty-two percent of the medical patients who required RRT did so during the first 2 d of intensive care, as compared with 19% of the surgical patients ($P = 0.0002$). The median day of the first RRT was 3 (2 to 6) in the medical ICU and 7 (3 to 12) in the surgical ICU ($P < 0.0001$). The first day of oliguria also occurred significantly earlier in the medical population (median 2 [range 1 to 5] versus 3 [1 to 9] in the surgical cohort; $P = 0.02$). After exclusion of 101 patients (16 surgical and 85 medical patients, 52 of whom were treated with IIT and 49 conventionally) who required RRT within the first 48 h after admission, the effect of IIT on the need for RRT became significant (decrease from 8.8 to 6.7%; $P = 0.05$).

The mean morning blood glucose level tended to be higher in patients who developed mR-I ($P = 0.07$) and was significantly higher in patients who developed mR-F (145 ± 39 versus 129 ± 37 mg/dl in those without mR-F; $P = 0.0008$) or mR-IF (138 ± 35 versus 129 ± 37 mg/dl in those without mR-IF; $P = 0.003$). This difference was not present in the outcome categories in which no beneficial effect was noted (oliguria, need for RRT). Comparison of different levels of glucose control (mean morning blood glucose level <110, 110 to 150, or >150 mg/dl) showed that normoglycemia results in the best protective effect on mR-IF (Figure 2). The mean daily dosage of insulin was

Table 3. Effect of IIT versus conventional treatment on the different renal outcome categories for the whole study population ($n = 2707$) and for the surgical ($n = 1540$) and medical cohort ($n = 1167$)

Outcome Parameter	n (%)	Intensive/Conventional (%); OR (95% CI)	P ^a	Surgical (n [%])	Intensive/Conventional (%); OR (95% CI)	P ^b	Medical (n [%])	Intensive/Conventional (%); OR (95% CI)	P ^c
mR-R	163 (6.4)	6.7/6.1; 1.11 (0.81 to 1.52)	0.5300	71 (4.8)	5.0/4.7; 1.09 (0.68 to 1.75)	0.730	92 (8.5)	9.0/8.1; 1.12 (0.73 to 1.71)	0.61
mR-I	101 (3.8)	3.0/6.1; 0.65 (0.43 to 0.97)	0.0300	48 (3.2)	2.4/3.9; 0.60 (0.33 to 1.08)	0.090	53 (4.7)	3.9/5.5; 0.69 (0.39 to 1.20)	0.19
mR-F	63 (2.3)	1.5/3.1; 0.47 (0.27 to 0.79)	0.0050	27 (1.8)	0.9/2.6; 0.35 (0.15 to 0.84)	0.020	36 (3.1)	2.2/3.9; 0.56 (0.28 to 1.11)	0.10
mR-IF	164 (6.1)	4.5/7.6; 0.57 (0.41 to 0.79)	0.0007	75 (4.9)	3.3/6.5; 0.50 (0.30 to 0.81)	0.005	89 (7.6)	6.0/9.2; 0.63 (0.40 to 0.98)	0.04
Oliguria	283 (10.5)	9.8/11.1; 0.88 (0.69 to 1.12)	0.3100	64 (4.2)	2.6/5.6; 0.45 (0.27 to 0.78)	0.004	219 (18.8)	19.2/18.3; 1.07 (0.79 to 1.43)	0.68
Need for RRT	291 (10.7)	9.9/11.6; 0.84 (0.66 to 1.07)	0.1700	88 (5.7)	4.0/7.4; 0.51 (0.33 to 0.81)	0.004	203 (17.4)	17.7/17.1; 1.04 (0.77 to 1.41)	0.79
AKI	516 (19.4)	18.3/19.8; 0.90 (0.75 to 1.09)	0.3000	183 (11.9)	10.0/13.7; 0.70 (0.51 to 0.96)	0.030	333 (28.5)	29.0/28.0; 1.05 (0.82 to 1.35)	0.70

^aP for the difference in the renal outcome between IIT and conventional treatment and for the respective OR for all patients.

^bP for the difference in the renal outcome between IIT and conventional treatment and the respective OR in surgical patients.

^cP for the difference in the renal outcome between IIT and conventional treatment and the respective OR in medical patients.

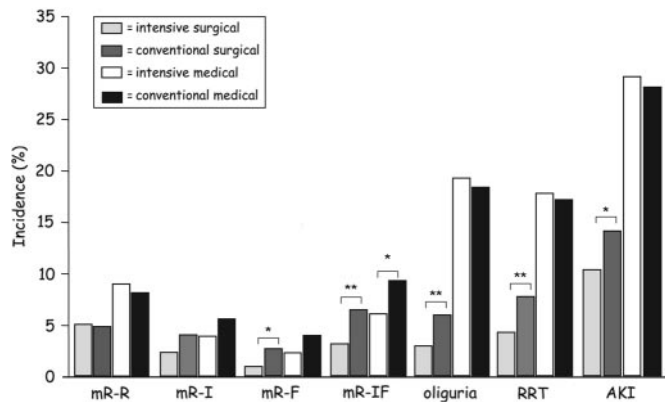


Figure 1. Impact of IIT versus conventional treatment on the incidence of different renal outcome categories in surgical and medical patients. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

significantly higher in patients with adverse renal outcome: 37.9 U/d (range 2.4 to 76.0 U/d) in patients who developed mR-IF as compared with 32.5 U/d (range 0.0 to 64.5 U/d) in those who did not ($P = 0.05$); 42.5 U/d (range 8.1 to 78.3 U/d) in patients who needed RRT versus 31.7 U/d (range 0.0 to 64.0 U/d) in those who did not ($P < 0.0001$); and 43.5 U/d (range 7.9 to 78.6 U/d) in patients who developed oliguria as compared with 31.8 U/d (range 0.0 to 63.8 U/d) in those without oliguria ($P < 0.0001$).

Mechanistic Analyses

Mechanistic analyses were performed only in the 354 surgical patients who required a prolonged ICU stay of >7 d. The renal outcome parameter used for this analysis was the development of mR-IF, which was reduced by IIT (OR 0.50; 95% CI 0.28 to 0.91; $P = 0.02$).

Lipids

IIT increased serum levels of LDL and HDL cholesterol and suppressed the elevated serum triglyceride concentrations.²⁷ On day 7, patients who developed mR-IF had lower LDL cholesterol (14 mg/dl [range 5 to 39 mg/dl] versus 39 mg/dl [range 19 to 61 mg/dl]; $P < 0.0001$), lower HDL cholesterol (10 mg/dl [range 7 to 16 mg/dl] versus 16 mg/dl [range 11 to 21 mg/dl]; $P < 0.0001$) and higher triglyceride levels (181 mg/dl [range 117 to 255 mg/dl] versus 130 mg/dl [range 94 to 191 mg/dl]; $P = 0.0006$). These lipid abnormalities were proportionally related to worsening RIFLE class as shown in Figure 3. When the lipid levels were entered into a logistic regression model together with the insulin treatment group, the impact of IIT on the LDL level seemed to explain statistically its beneficial effect on renal outcome (Table 4).

Markers of Endothelial Activation

The effect of IIT on markers of endothelial function has been described previously (attenuated rise in intercellular adhesion molecule [ICAM] and trend to lower E-selectin).²⁸ Patients who developed mR-IF had higher day 7 levels of ICAM-1 (777

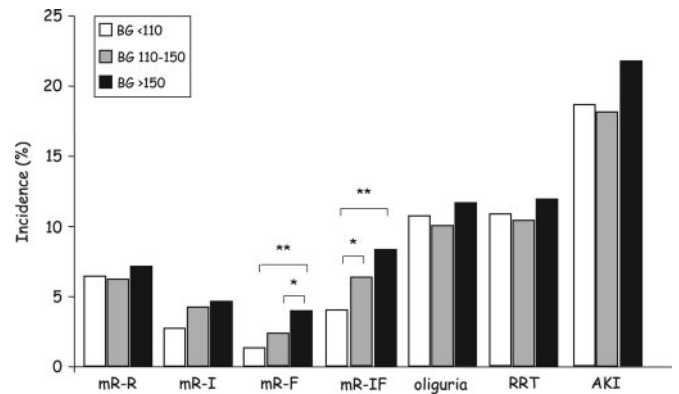


Figure 2. Impact of the level of glucose control on the different renal outcome categories. □, Patients with a mean blood glucose level <110 mg/dl; ▨, patients with mean blood glucose level between 110 and 150 mg/dl; ■, patients with mean blood glucose level >150 mg/dl. * $P < 0.05$; ** $P < 0.01$.

ng/ml [range 552 to 1076 ng/ml] versus 564 ng/ml [range 405 to 871 ng/ml]; $P = 0.0003$) and E-selectin (55 ng/ml [range 43 to 83 ng/ml] versus 44 ng/ml [range 32 to 60 ng/ml]; $P = 0.0001$). In a multivariate logistic regression model with IIT, both endothelial markers were independently associated with development of mR-IF (Table 4).

Nitric Oxide

As previously reported, IIT significantly decreased the level of nitric oxide (NO) at day 7.²⁸ Patients who developed mR-IF also had higher NO levels on day 7 (46 μ M [range 33 to 75 μ M] versus 22 μ M [range 13 to 35 μ M]; $P < 0.0001$). This NO level seemed to be significantly associated with the development of mR-IF, and its introduction into the regression model statistically explained the association between IIT and mR-IF (Table 4).

DISCUSSION

This secondary analysis of two large, prospective, randomized clinical trials showed that IIT aiming at normoglycemia protects the kidney of mixed medical/surgical ICU patients. IIT reduced the incidence of mR-I and mR-F but did not affect the mildest form of mR-R or the presence of oliguria or the need for RRT. The renoprotective effect was more pronounced in surgical than in medical patients. In the surgical patients, IIT also significantly reduced the presence of oliguria and the need for RRT.

The diagnosis of AKI was based on the recently published RIFLE criteria,²⁹ with, however, the admission serum creatinine as the "baseline" value. This definition will therefore not capture patients who already sustained AKI before ICU admission and presented with increased serum creatinine. Our modification of the RIFLE definition, explains why we found lower incidences and higher mortalities for the different mRIFLE

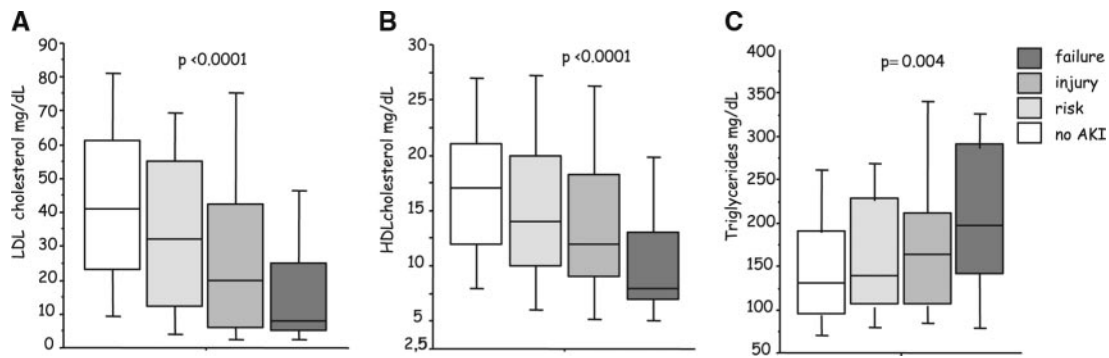


Figure 3. Circulating lipids levels (median and interquartile range) on day 7 of ICU stay in patients without AKI, mR-R, mR-I, and mR-F. (A) LDL cholesterol. (B) HDL cholesterol. (C) Triglycerides.

Table 4. Logistic regression evaluating the association between biochemical variables and the development of mR-IF in patients who were treated for at least 7 d ($n = 354$)^a

Parameter	OR	95% CI	P
Lipid variables			
IIT versus CIT ^b	0.500	0.28 to 0.91	0.0220
IIT versus CIT ^c	0.690	0.37 to 1.29	0.2400
triglycerides (per mg/dl added)	1.002	0.99 to 1.005	0.3200
LDL ≤ 15 mg/dl (versus > 15 mg/dl)	2.640	1.29 to 5.40	0.0080
HDL ≤ 12 mg/dl (versus > 12 mg/dl)	1.740	0.82 to 3.69	0.1500
Markers of endothelial activation			
IIT versus CIT ^b	0.500	0.28 to 0.91	0.0220
IIT versus CIT ^c	0.580	0.31 to 1.08	0.0900
ICAM > 600 ng/dl (versus ≤ 600 ng/dl)	2.150	1.13 to 4.07	0.0200
E-selectin (per ng/ml added)	1.017	1.006 to 1.027	0.0015
NO			
IIT versus CIT ^b	0.500	0.28 to 0.91	0.0220
IIT versus CIT ^c	0.620	0.33 to 1.17	0.1400
NO level > 40 μ M (versus ≤ 40 μ M)	5.590	3.09 to 10.1	< 0.0001

^aCIT, conventional insulin therapy.

^bOnly IIT versus CIT entered into the model.

^cWith addition of the biochemical variable.

classes than was recently published³⁰; however, the main purpose of this study was to evaluate the effect of a treatment started at ICU admission, and using changes from admission creatinine is therefore more appropriate. As in previous studies, increasing RIFLE class was significantly associated with mortality.^{30–35}

IIT during intensive care is a protective strategy that prevents secondary complications and thus, evidently, cannot prevent damage that is already present upon ICU admission. This explains why the effect was more pronounced in the surgical than in the medical ICU patients. Indeed, the medical patients were more severely ill on ICU admission with, in particular, a higher admission creatinine. More than 35% of the medical patients who required RRT did so during the first 2 d of ICU treatment, and for the development of oliguria, it was even more than 45%; however, using the outcome categories that are defined using changes from baseline, even in this very sick medical population, IIT prevented further kidney injury that occurs during ICU stay. Omitting patients who required early RRT also showed a beneficial effect of IIT on this outcome category.

Possible explanations for the renoprotective effect are a direct effect of the intervention on the kidney and/or an indirect effect *via* prevention of complications. Furthermore, the benefit may be related to prevention of glucose toxicity or to a glycemia-independent action of insulin. Sepsis and hypotension are the main causes of AKI in critically ill patients.³⁶ IIT does not detectably exert hemodynamic effects.²⁴ Because hyperglycemia affects all major components of innate immunity,³⁷ achieving normoglycemia may have reduced sepsis-induced AKI. Although the surgical study indeed showed a significant reduction of bacteremia, of excessive inflammation, and of septic multiple organ dysfunction syndrome-related deaths,²⁴ this specific sepsis-induced morbidity prevention could not be confirmed in the study of medical ICU patients, which, conversely, also showed renal protection by IIT.²⁵

Despite the kidneys being the main organ for insulin disposal,³⁸ the mean dosage of insulin was significantly higher in patients with mR-IF, need for RRT, and oliguria. This probably reflects a more severe insulin resistance in the sicker patients and does not allow conclusions about a direct effect of insulin on the kidney.

Although the mean morning blood glucose level was significantly higher in patients with AKI, the complex renal handling of glucose (filtration, reabsorption, transport maximum, gluconeogenesis, oxidation) may obscure the cause–effect relationship between blood glucose and AKI. Because of the difficulty of dissociating the effect of insulin from that of glucose control in the clinical setting, blood glucose and insulin levels were manipulated independently in a rabbit model of critical illness. This experiment clearly showed that prevention of AKI requires maintaining normoglycemia and is independent of insulin levels.³⁹ The importance of achieving normoglycemia is illustrated by the effect of different levels of glucose control on the renal outcome parameters.

A possible indirect mechanism of benefit to the kidney involves the metabolic insulin actions on lipid metabolism. Critical illness is associated with dyslipidemia, characterized by hypocholesterolemia, both LDL and HDL cholesterol, and hypertriglyceridemia.⁴⁰ IIT has been shown to improve this lipid profile.²⁷ This analysis does not substantiate a cause–effect relationship but at least suggests that the improved lipid profile and especially the elevation of the LDL levels may represent one potential mechanism for the renoprotective effect of IIT, consistent with previous observations in an animal model of renal ischemia-reperfusion.⁴¹

The exact mechanism by which maintaining normoglycemia protects the kidney will be difficult to unravel, because the kidney is a complex organ composed of heterogeneous cells that perform various tasks. Diabetes selectively damages cells that do not respond to hyperglycemia by reducing glucose transport, such as endothelial cells. The role of the endothelium in the pathogenesis of ischemia-reperfusion–induced AKI is increasingly recognized.⁴² Animal experiments have found a renoprotective effect of antibodies to ICAM-1 and antisense oligonucleotides for ICAM-1 in ischemic injury,^{43–45} and the same has been shown for E-selectin inhibition.^{46,47} The previously reported protective effect of IIT on the endothelium,²⁸ might therefore be an important pathway of renoprotection, which is suggested by the higher levels of ICAM-1 and E-selectin in patients who develop AKI, although the latter might also result from reduced renal clearance.

Hyperglycemia favors the increased expression of the inducible isoform of NO synthase through the activation of NF- κ B, resulting in high NO levels. In this analysis, patients with AKI had a higher level of NO that in multivariate logistic regression was significantly associated with AKI and explained, at least partially, the effect of IIT. Although not supporting a cause–effect relationship, this association suggests an impact of IIT on another damaging pathway associated with AKI.^{48,49}

This study has some limitations that need to be highlighted. In both randomized trials, kidney injury was a secondary, not the primary, outcome measure. It is, however, questionable whether a similar study, with AKI as primary outcome, will ever be performed. We did not perform correction for multiple comparisons, and some of the subgroups had limited sample size, reducing the power of the conclusions; however, the

overall trend of the results clearly suggests a renoprotective effect of IIT.

In conclusion, this secondary analysis of two large RCT showed that IIT targeting normoglycemia protects the kidney of critically ill patients. Because it concerns a preventive, not a therapeutic, strategy, the benefit is more pronounced in surgical than in medical patients, because the latter frequently presented with kidney injury upon admission. An improved lipid profile, endothelial protection, and reduced NO levels might contribute to the observed effect.

CONCISE METHODS

Study Population

This analysis included 1540 mechanically ventilated adult patients who were admitted to a mainly surgical ICU and 1167 patients who were assumed to require at least a third day of intensive care in a medical ICU. As compared with the original study populations,^{24,25} this analysis excluded 41 patients with ESRD (eight surgical and 33 medical patients). Written informed consent was obtained from the closest family member. The study protocol was approved by the institutional ethical review board. The study followed the Declaration of Helsinki and good clinical practice guidelines.

Study Design

The detailed study protocol has been described elsewhere.^{24,25} In brief, at ICU admission, patients were randomly assigned to either IIT or conventional insulin treatment. Insulin was always given by continuous infusion, and blood glucose levels were measured every 2 to 4 h. In the IIT group, the insulin infusion was titrated to achieve blood glucose levels between 80 and 110 mg/dl. In the conventional treatment group, the insulin infusion was started only when blood glucose exceeded 215 mg/dl and titrated to keep the level between 180 and 200 mg/dl. The infusion was decreased and eventually stopped when blood glucose fell below 180 mg/dl. This protocol resulted in a mean blood glucose level of 106 mg/dl in the IIT group and 152 mg/dl in the conventional treatment group. Daily urine output was recorded, and biochemical analyses were performed on daily morning blood samples.

Baseline demographic and clinical data were recorded, including age, gender, body mass index, diagnostic category, and history of diabetes or malignancy. Severity of illness upon ICU admission was quantified by the APACHE II score. The primary outcome of the original studies was mortality. Secondary end points were duration of intensive care and ventilatory support; newly acquired kidney injury; the need for RRT, for vasopressors or inotropes, or for red blood cell transfusion; critical illness polyneuropathy; bacteremia; hyperinflammation (peak C-reactive protein level); and hyperbilirubinemia.

For this analysis, renal dysfunction was specified using mRIFLE criteria.²⁹ Serum creatinine was determined daily and mR-R was defined as a peak over admission creatinine ratio between 1.5 and 1.99, mR-I as a peak over admission creatinine ratio between 2 and 2.99, and mR-F as a peak over admission creatinine ratio of >3 . The original publications defined “newly acquired kidney injury” as at least a

doubling of the admission creatinine level (or the combination of mR-I and mR-F). Because the database did not contain hourly urine output, oliguria was defined as a urine output of <400 ml/d at any day during ICU stay. The need for RRT was determined by the treating physician. Patients were defined as having AKI when any of the aforementioned adverse renal outcomes was present. For patients who required RRT, renal recovery was defined as being independent of RRT at hospital discharge.

Mechanistic Analyses

Markers of endothelial activation, inflammatory cytokines, and lipid abnormalities, obtained during previous studies in surgical patients with prolonged ICU stay,^{27,28} were used to address potential mechanisms behind the renoprotective effect of IIT. Circulating levels of ICAM-1, E-selectin, NO, triglycerides, and HDL and LDL cholesterol had been determined on admission day and on day 7. The methods of these biochemical analyses have been described in detail elsewhere.^{27,28}

Statistical Analyses

Statview 5.01 software (SAS Institute, Cary, NC) for Macintosh was used for statistical analysis. The data are presented as means \pm SD, median (interquartile range), or percentages. The *t* test was used for comparison of normally distributed data (skewness below 1) and the Mann-Whitney *U* test for not normally distributed data. Proportions were compared with the χ^2 test. OR and 95% CI were determined with logistic regression analysis. To determine whether the renoprotective effect of IIT could be explained by its effect on circulating NO levels, cytokine levels, lipids, and markers of endothelial activation, we used logistic regression models introducing both the treatment group and the "biochemical" variables. Variables that did not show a linear correlation with the studied outcome were dichotomized. Statistical significance was assumed for $P < 0.05$. *P* values were not corrected for multiple comparisons.

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