Podejście restrykcyjne czy liberalne?

Od Van den Berghe do NICE Sugar study

Piotr Knapik

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Fakty

- hiperglikemia i oporność na insulinę są powszechne u chorych w stanie krytycznym, nawet jeżeli nie występowała u nich wcześniej cukrzyca,
- w warunkach niedokrwienia i stresu metabolizm glukozy jest zwolniony i ulega przesunięciu w stronę glikolizy beztlenowej,
- odpowiednia podaż insuliny umożliwia prawidłowe wykorzystanie glukozy przez miocyty.

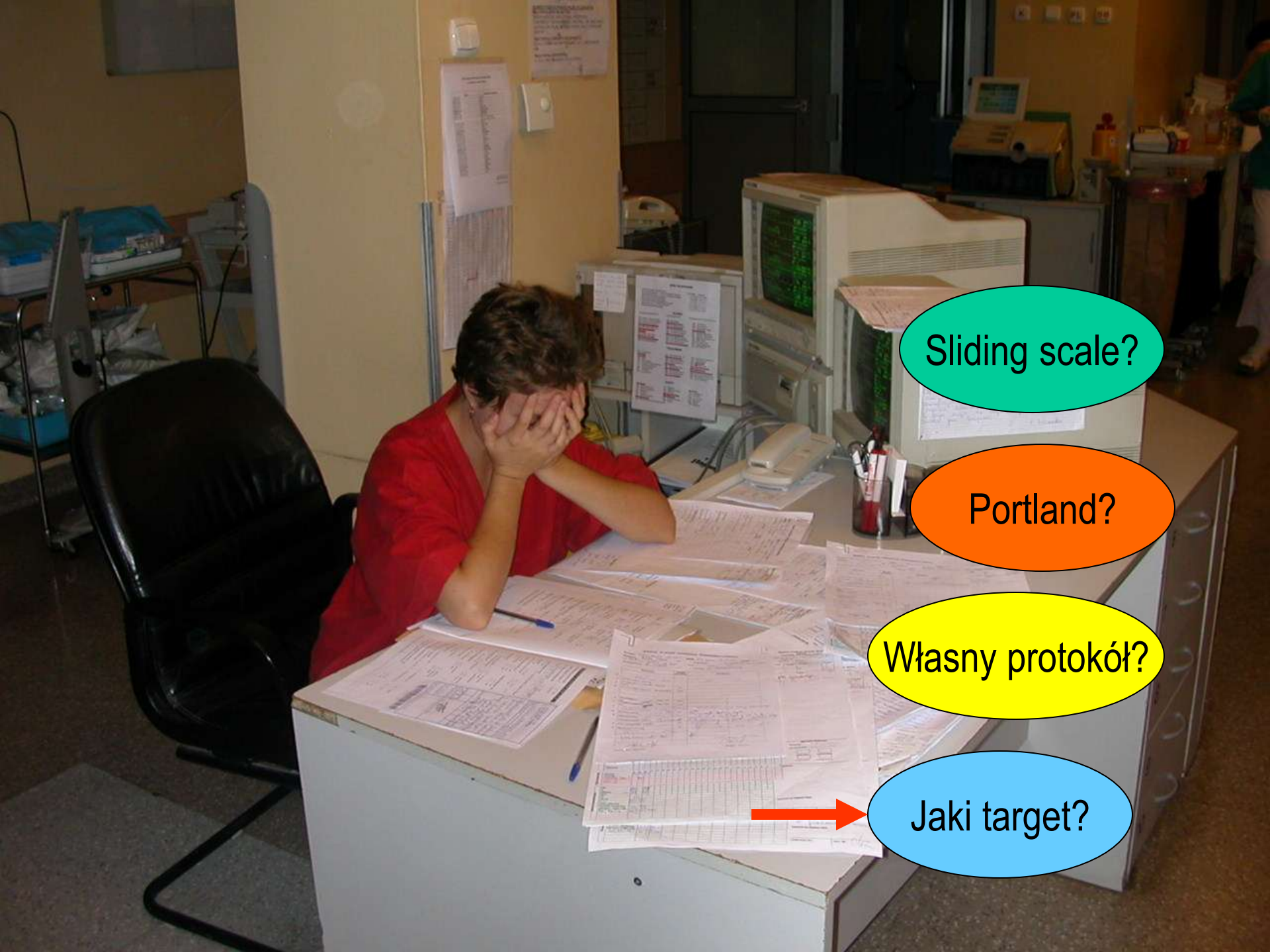
Hiperglikemia jest szkodliwa i niebezpieczna

Efekty:

- dysfunkcja śródbłonka naczyniowego – działa prozakrzepowo
- zmiana metabolizmu z glukozy na rzecz kwasów tłuszczowych - zwiększenia ilość toksycznych metabolitów kwasów tłuszczowych
- zwiększone zużycie tlenu przez mięsień sercowy

Mc Nulty P et al, J.Cardiothorac Vasc Anesth, 2001, 15, 768.

Hiperglikemia jest powszechna u krytycznie chorych


Sliding scale?
Portland?
Własny protokół?
Jaki target?

The New England Journal of Medicine

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INTENSIVE INSULIN THERAPY IN CRITICALLY ILL PATIENTS

GREET VAN DEN BERGHE, M.D., PH.D., PIETER WOUTERS, M.SC., FRANK WEEKERS, M.D., CHARLES VERWAEST, M.D., FRANS BRUYNINCKX, M.D., MIET SCHETZ, M.D., PH.D., DIRK VLASSELAERS, M.D., PATRICK FERDINANDE, M.D., PH.D., PETER LAUWERS, M.D., AND ROGER BOUILLON, M.D., PH.D.

Założenia pracy

- wszyscy dorośli pacjenci przyjęci do jednego dużego oddziału intensywnej terapii wymagający mechanicznej wentylacji w 2000 roku
- w ciągu jednego roku do badania zakwalifikowano 1548 osób
- randomizacja następowała w chwili przyjęcia do OIT

Grupy badane

- grupa badana – początek wlewu insuliny jeżeli glikemia >110 mg% i utrzymanie glikemii w przedziale 80-110 mg% (n=765)
- grupa kontrolna – początek wlewu insuliny jeżeli glikemia >215% i utrzymanie glikemii w przedziale 180-200 mg% (n=783)

Chorzy

- wszyscy chorzy otrzymywali 200-300 g glukozy na dobę w ciągłym wlewie dożylnym,
- w każdej grupie było po 13% chorych z cukrzycą
- główne punkty końcowe: zgon w OIT, zgon szpitalny, pobyt w OIT>14 dni, ponowne przyjęcie do OIT,
- inne punkty końcowe: konieczność zastosowania terapii nerkozastępczej, wsparcie aminami katecholowymi, polineuropatia stanu krytycznego i wiele innych.

Populacja – w większości chorzy po zabiegach operacyjnych!

CHARACTERISTIC	CONVENTIONAL TREATMENT (N=783)	INTENSIVE TREATMENT (N=765)
Male sex — no. (%)	557 (71)	544 (71)
Age — yr	62.2±13.9	63.4±13.6
Body-mass index†	25.8±4.7	26.2±4.4
Reason for intensive care — no. (%)		
Cardiac surgery	493 (63)	477 (62)
Noncardiac indication	290 (37)	288 (38)
Neurologic disease, cerebral trauma, or brain surgery	30 (4)	33 (4)
Thoracic surgery, respiratory insufficiency, or both	56 (7)	66 (9)
Abdominal surgery or peritonitis	58 (7)	45 (6)
Vascular surgery	32 (4)	30 (4)
Multiple trauma or severe burns	35 (4)	33 (4)
Transplantation	44 (6)	46 (6)
Other	35 (4)	35 (5)

TABLE 2. INSULIN THERAPY AND CONTROL OF BLOOD GLUCOSE LEVELS.*

VARIABLE	CONVENTIONAL TREATMENT (N=783)	INTENSIVE TREATMENT (N=765)	P VALUE†
Administration of insulin — no. (%)	307 (39.2)	755 (98.7)	<0.001
Insulin dose — IU/day‡			
Median	33	71	
Interquartile range	17–56	48–100	<0.001
Duration of insulin use — % of ICU stay			
Median	67	100	<0.001
Interquartile range	40–100		
Morning blood glucose — mg/dl§			
All patients	153±33	103±19	<0.001
Patients receiving insulin	173±33	103±18	<0.001

TABLE 3. MORTALITY.

VARIABLE	CONVENTIONAL TREATMENT (N=783)	INTENSIVE TREATMENT (N=765)	P VALUE*
Death during intensive care — no./total no. (%)	63/783 (8.0)	35/765 (4.6)	<0.04 (adjusted)
During first 5 days of intensive care	14/783 (1.8)	13/765 (1.7)	0.9
Among patients receiving intensive care for >5 days	49/243 (20.2)	22/208 (10.6)	0.005
Reason for intensive care			
Cardiac surgery	25/493 (5.1)	10/477 (2.1)	
Neurologic disease, cerebral trauma, or brain surgery	7/30 (23.3)	6/33 (18.2)	
Thoracic surgery, respiratory insufficiency, or both	10/56 (17.9)	5/66 (7.6)	
Abdominal surgery or peritonitis	9/58 (15.5)	6/45 (13.3)	
Vascular surgery	2/32 (6.2)	2/30 (6.7)	
Multiple trauma or severe burns	3/35 (8.6)	4/33 (12.1)	
Transplantation	1/44 (2.3)	2/46 (4.4)	
Other	6/35 (17.1)	0/35	
No history of diabetes	57/680 (8.4)	31/664 (4.7)	
No history of diabetes and >5 days of intensive care	45/218 (20.6)	20/187 (10.7)	
History of diabetes	6/103 (5.8)	4/101 (4.0)	
History of diabetes and >5 days of intensive care	4/25 (16.0)	2/21 (9.5)	
Cause of death — no.			0.02
Multiple-organ failure with proven septic focus	33	8	
Multiple-organ failure without detectable septic focus	18	14	
Severe brain damage	5	3	
Acute cardiovascular collapse	7	10	
In-hospital death — no./total no. (%)			
All patients	85/783 (10.9)	55/765 (7.2)	0.01
Patients receiving intensive care for >5 days	64/243 (26.3)	35/208 (16.8)	0.01

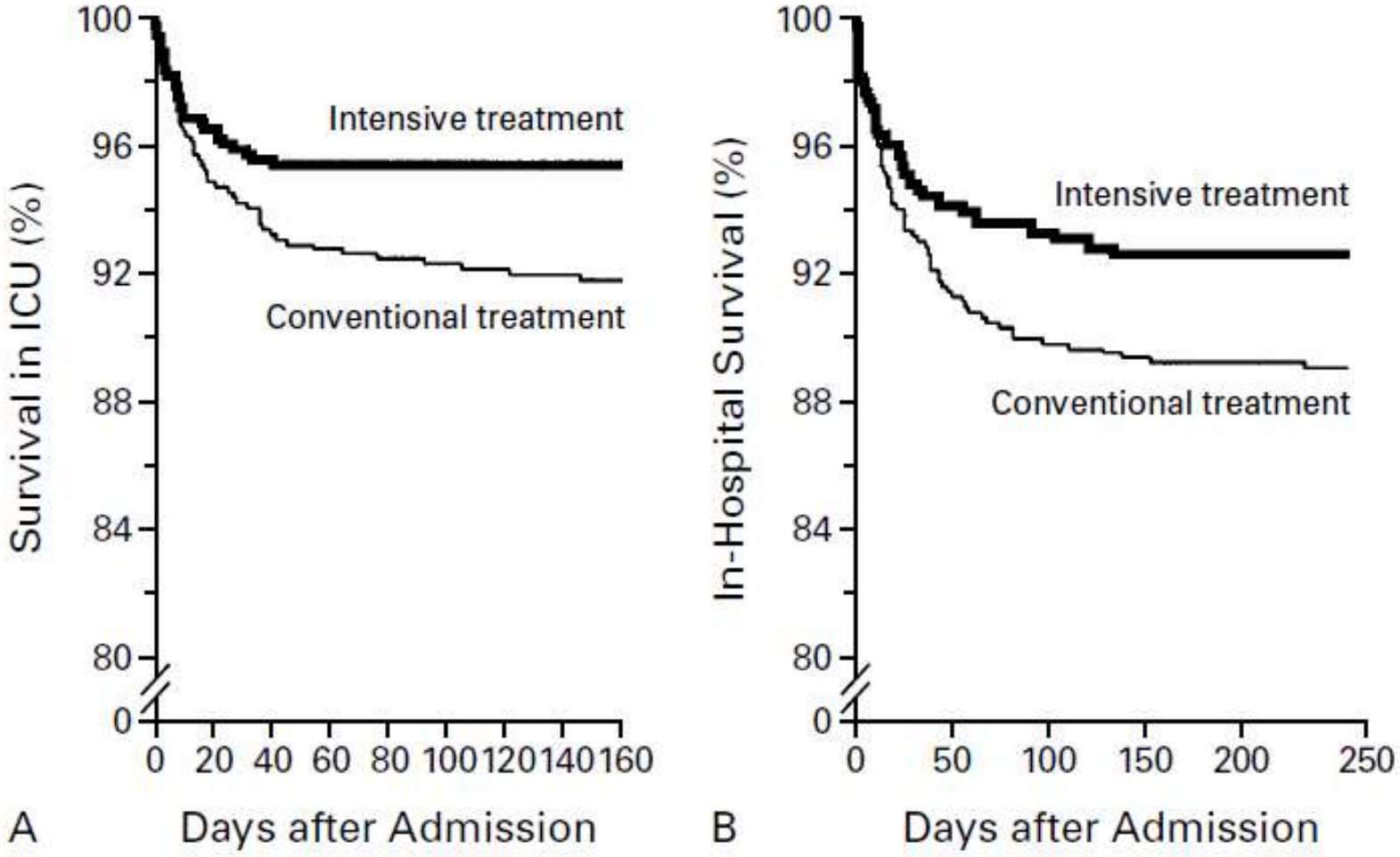
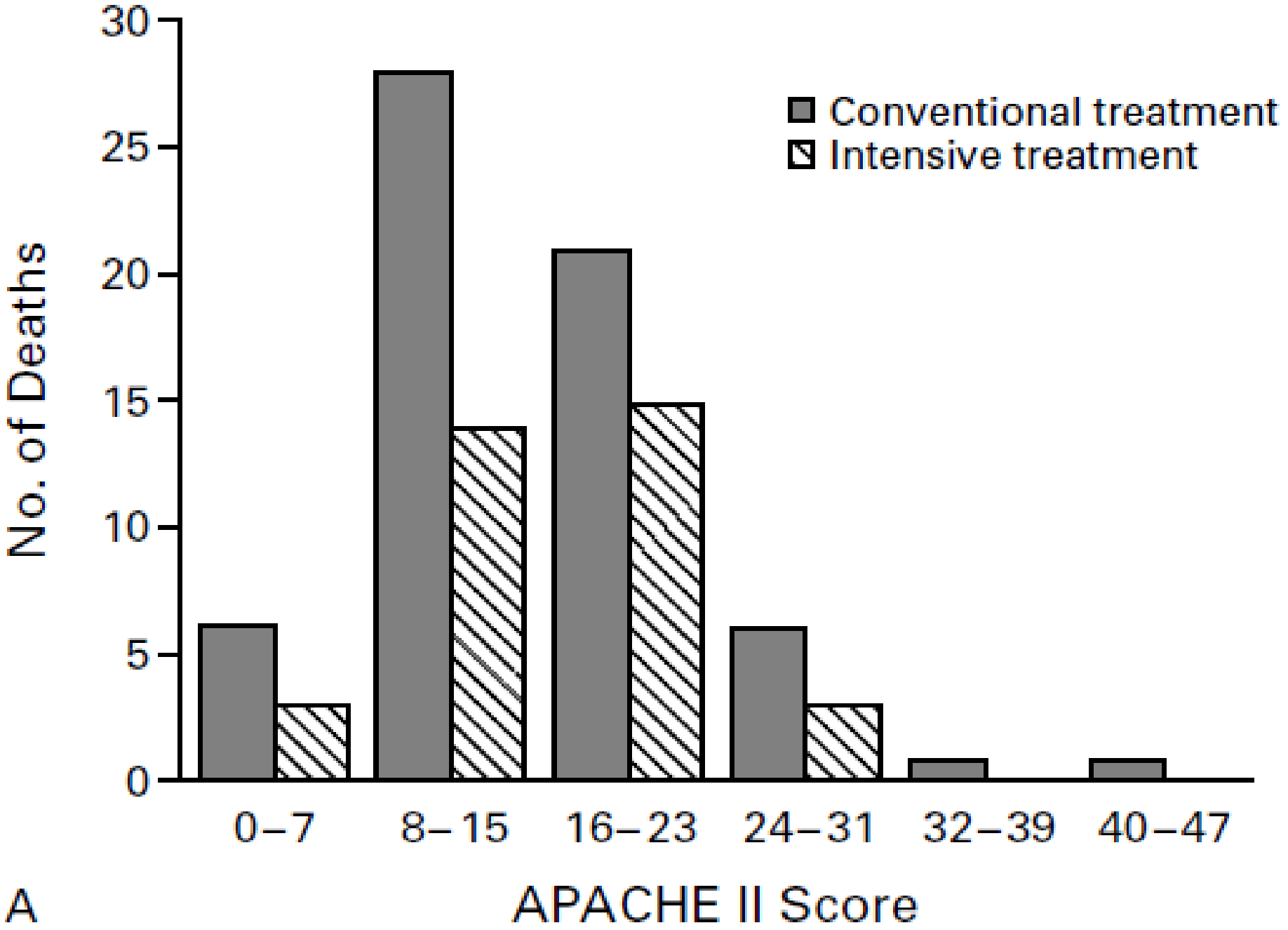


Figure 1. Kaplan–Meier Curves Showing Cumulative Survival of Patients Who Received Intensive Insulin Treatment or Conventional Treatment in the Intensive Care Unit (ICU).

Patients discharged alive from the ICU (Panel A) and from the hospital (Panel B) were considered to have survived. In both cases, the differences between the treatment groups were significant (survival in ICU, nominal $P=0.005$ and adjusted $P<0.04$; in-hospital survival, nominal $P=0.01$). P values were determined with the use of the Mantel–Cox log-rank test.


30
25
20
15
10
5
0
No. of Deaths
Conventional treatment
Intensive treatment
0–7
8–15
16–23
24–31
32–39
40–47
APACHE II Score

A

upłynęło kilka lat i...

The NEW ENGLAND JOURNAL of MEDICINE

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Intensive versus Conventional Glucose Control in Critically Ill Patients

The NICE-SUGAR Study Investigators*

Założenia pracy

- wszyscy dorośli pacjenci przyjęci do 42 oddziałów intensywnej terapii na terenie Australii i Nowej Zelandii wymagający pobytu w obszarze intensywnej terapii przez co najmniej 72 godziny w latach 2004-2008
- w ciągu 4 lat do badania zakwalifikowano 6104 osoby
- randomizacja następowała w chwili przyjęcia do OIT

4x więcej chorych!

APPENDIX

The affiliations of the NICE-SUGAR writing committee members are as follows: Royal North Shore Hospital (S.F.) and the George Institute for International Health, University of Sydney, Sydney (S.F., S.Y.-S.S., D.B, S.H., R.N.); Vancouver Coastal Health (D.R.C.), University of British Columbia (D.F.), and Vancouver General Hospital, University of British Columbia (V.D.) — all in Vancouver, BC, Canada; Austin Hospital, Melbourne University, Melbourne, VIC, Australia (R.B.); McMaster University, Hamilton, ON, Canada (D.C., E.M.); St. Paul's Hospital and University of British Columbia, Vancouver, BC, Canada (P.D.); Vancouver General Hospital, Vancouver Coastal Health Research Institute, University of British Columbia, Vancouver, BC, Canada (W.R.H.); Ottawa Health Research Institute, the University of Ottawa, Ottawa (P.C.H.); Queen's University, Kingston, ON, Canada (D.K.H.); Auckland City Hospital, Auckland, New Zealand (C.M.); Canberra Hospital and Australian National University, Canberra, ACT, Australia (I.M.); St. George Hospital and the George Institute for International Health, University of New South Wales, Sydney (J.M.); Royal North Shore Hospital, University of Sydney, Sydney (J.P.); Kolling Institute of Medical Research, Royal North Shore Hospital and the University of Sydney, Sydney (E.G.R.); Vancouver General Hospital and University of British Columbia, Vancouver, BC, Canada (J.J.R.). 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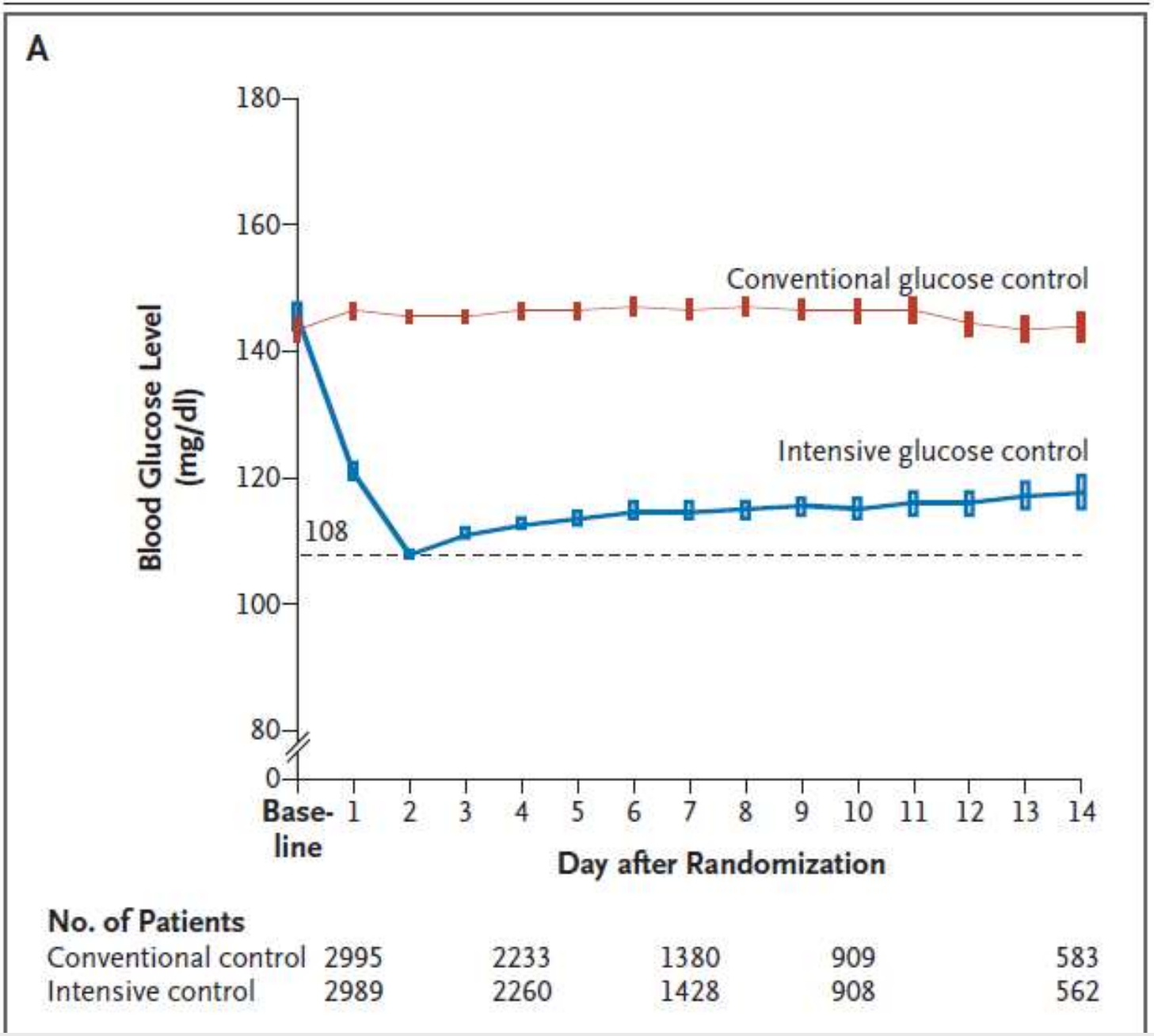
Grupy badane

- grupa badana – początek wlewu insuliny jeżeli glikemia >110 mg% i utrzymanie glikemii w przedziale 81-108 mg% (n=3054)
- grupa kontrolna – początek wlewu insuliny jeżeli glikemia >180% i utrzymanie glikemii w przedziale 140-180 mg% (n=3050)
- spadek glikemii<40mg% rejestrowano jako poważne zdarzenie niepożądane

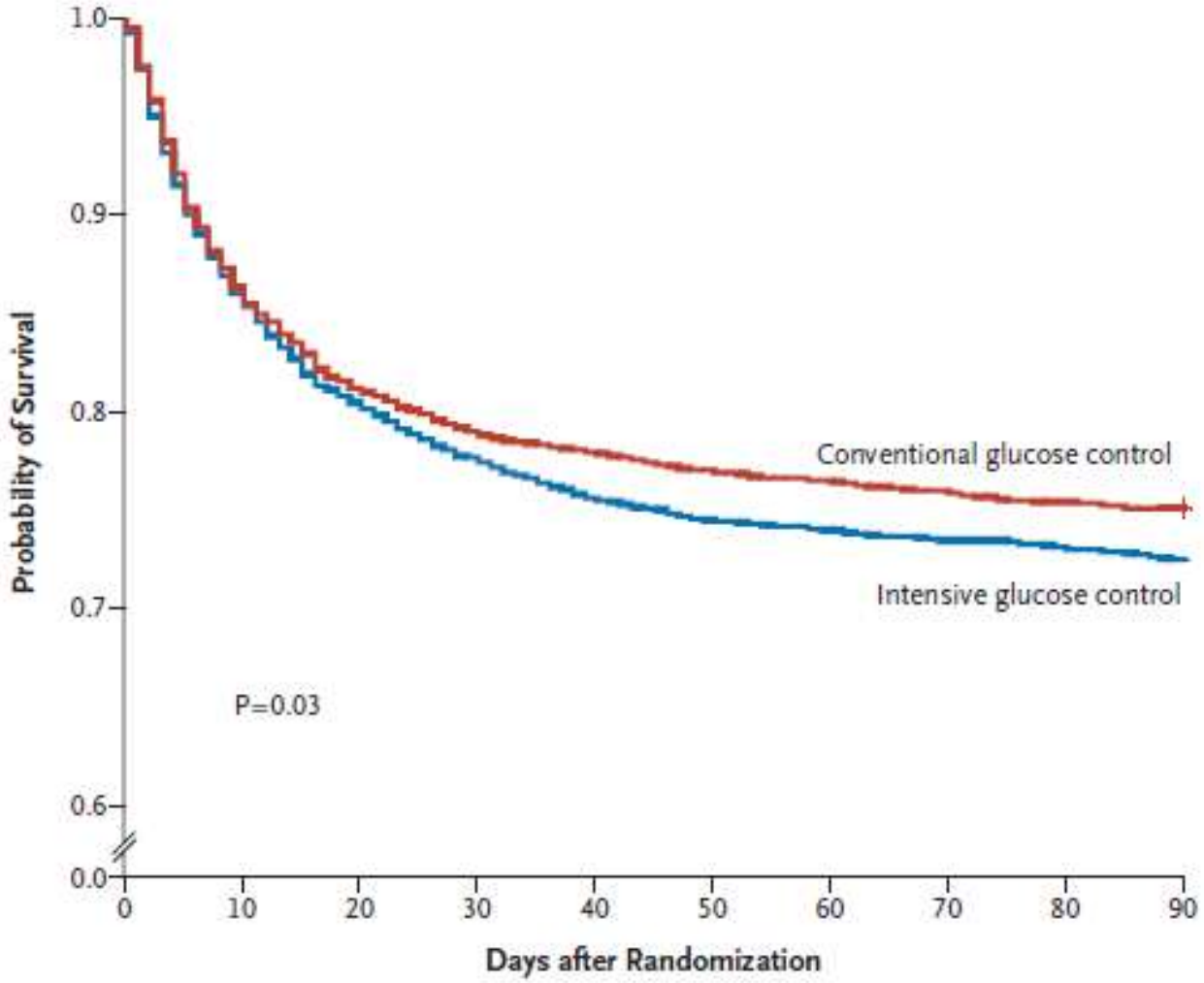
Variable	Intensive Glucose Control	Conventional Glucose Control
Mechanical ventilation — no./total no. (%)	2825/3014 (93.7)	2793/3014 (92.7)
Renal-replacement therapy — no./total no. (%)	179/3014 (5.9)	165/3014 (5.5)
History of diabetes mellitus — no./total no. (%)	615/3015 (20.4)	596/3014 (19.8)
Type I diabetes	50/615 (8.1)	42/596 (7.0)
Type II diabetes	565/615 (91.9)	554/596 (93.0)
Previous treatment with insulin	183/615 (29.8)	163/596 (27.3)
Previous treatment with systemic corticosteroids — no./total no. (%)	393/3014 (13.0)	378/3014 (12.5)
Subgroup classification — no./total no. (%)		
Severe sepsis at randomization	676/3014 (22.4)	626/3014 (20.8)
Trauma	422/3014 (14.0)	466/3014 (15.5)
APACHE II score ≥25	929/3013 (30.8)	945/3012 (31.4)

Table 3. Outcomes and Adverse Events.*

Outcome Measure	Intensive Glucose Control	Conventional Glucose Control	Odds Ratio or Absolute Difference (95% CI)†	Statistical Test	P Value
Death — no. of patients/total no. (%)				Logistic regression	
At day 90	829/3010 (27.5)	751/3012 (24.9)	1.14 (1.02 to 1.28)		0.02
At day 28	670/3010 (22.3)	627/3012 (20.8)	1.09 (0.96 to 1.23)		0.17
Severe hypoglycemia — no. of patients/total no. (%)	206/3016 (6.8)	15/3014 (0.5)	14.7 (9.0 to 25.9)	Logistic regression	<0.001


A
180
160
140
120
100
80
0
Blood Glucose Level (mg/dl)
Conventional glucose control
Intensive glucose control
108
Base-line
1
2
3
4
5
6
7
8
9
10
11
12
13
14
Day after Randomization
No. of Patients
Conventional control 2995 2233 1380 909 583
Intensive control 2989 2260 1428 908 562

A

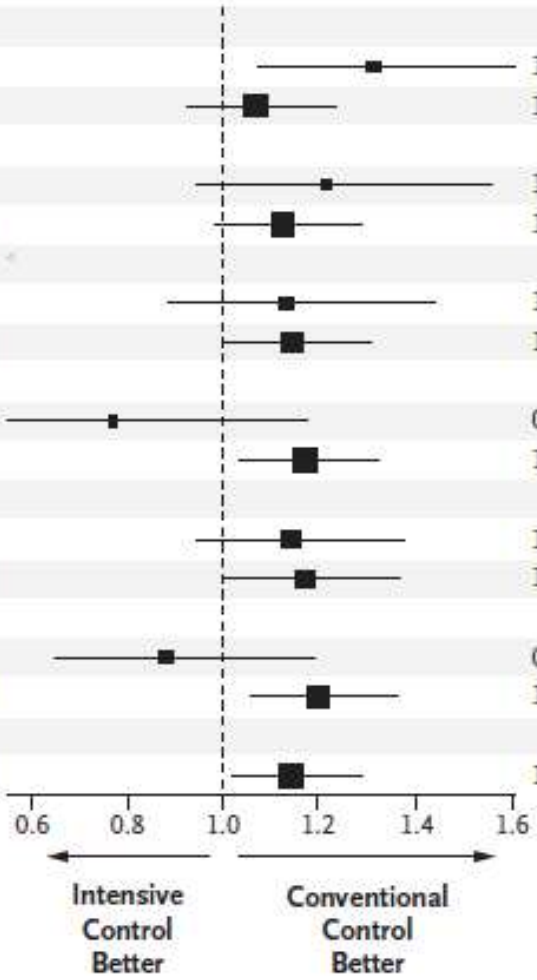


No. at Risk

Conventional control	3014	2379	2304	2261
Intensive control	3016	2337	2227	2182

B

Subgroup	Intensive Control (N=3010)	Conventional Control (N=3012)	Odds Ratio for Death (95% CI)	P Value for Heterogeneity
	no. of deaths/no. with data available			
Operative admission				0.10
Yes	272/1111	222/1121	1.31 (1.07–1.61)	
No	557/1898	529/1891	1.07 (0.93–1.23)	
Diabetes				0.60
Yes	195/615	165/596	1.21 (0.95–1.55)	
No	634/2394	586/2416	1.12 (0.99–1.28)	
Severe sepsis				0.93
Yes	202/673	172/626	1.13 (0.89–1.44)	
No	627/2335	579/2386	1.15 (1.01–1.31)	
Trauma				0.07
Yes	41/421	57/465	0.77 (0.50–1.18)	
No	788/2587	694/2547	1.17 (1.04–1.32)	
APACHE II score				0.84
≥25	386/927	363/944	1.14 (0.95–1.37)	
<25	442/2080	387/2066	1.17 (1.01–1.36)	
Corticosteroids				0.06
Yes	134/392	140/378	0.88 (0.66–1.19)	
No	695/2616	611/2634	1.20 (1.06–1.36)	
All deaths at day 90	829/3010	751/3012	1.14 (1.02–1.28)	0.02



Diabeł tkwi w szczegółach?

		Van den Berghe *et al.*[2]	Van den Berghe *et al.*[3]	NICE-SUGAR[8]
Number of eligible patients		1,562	2,110	7,294
Number of patients included		1,548	1,200	6,022
Percentage of medical patients		0	100	62.9
Percentage of surgical / postoperative admissions		96.0	0	37.1
Mean admission APACHE II score		9.0	23.0	21.1
Percentage of calories given intravenously		87.0	87.0	29.5
Target control (mM)		10.1-11.1	10.1-11.1	7.8-10.0
Target IIT (mM)		4.4-6.1	4.4-6.1	4.4-6.1
BG values reached [mM - mean (SD) or median (IQR 25-75)]	Control	8.5+/-1.8	8.5+/-1.7	8.1+/-1.4
	IIT	5.7+/-1.1	6.1+/-1.6	6.6+/-1.4

		Van den Berghe *et al.*[2]	Van den Berghe *et al.*[3]	NICE-SUGAR[8]
Mortality rate (%)		8.0	26.8	24.9
Hypoglycemia rate (%)	Control	0.8	3.1	0.5
	IIT	5.0	18.7	6.8
Mean amount of insulin infused (U/day)	Control	33	10	17
	IIT	71	59	50
Percentage of patients treated with insulin	Control	39	70	69
	IIT	99	98	97
Percentage of patients with preexisting diabetes		13	17	20

Intensywna kontrola glikemii:

- lepsza (Van den Berghe 1)
- bez różnicy (Van den Berghe 2)
- gorsza (NICE-Sugar)

Lena et al. Anesthesiology 2011; 114: 438.

???

Conclusions Intensive insulin therapy to maintain blood glucose at or below 110 mg per deciliter reduces morbidity and m ill patients in the d 20

Jaka glikemia jest optymalna?

In glucose control incre target of 180 mg or less per deciliter re did a target of 81 to 108 mg per deciliter. (ClinicalTrials.gov number, NCT00220987.)