

Intensive care

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Overview : Intensive insulin (glucose control) therapy in critical illness

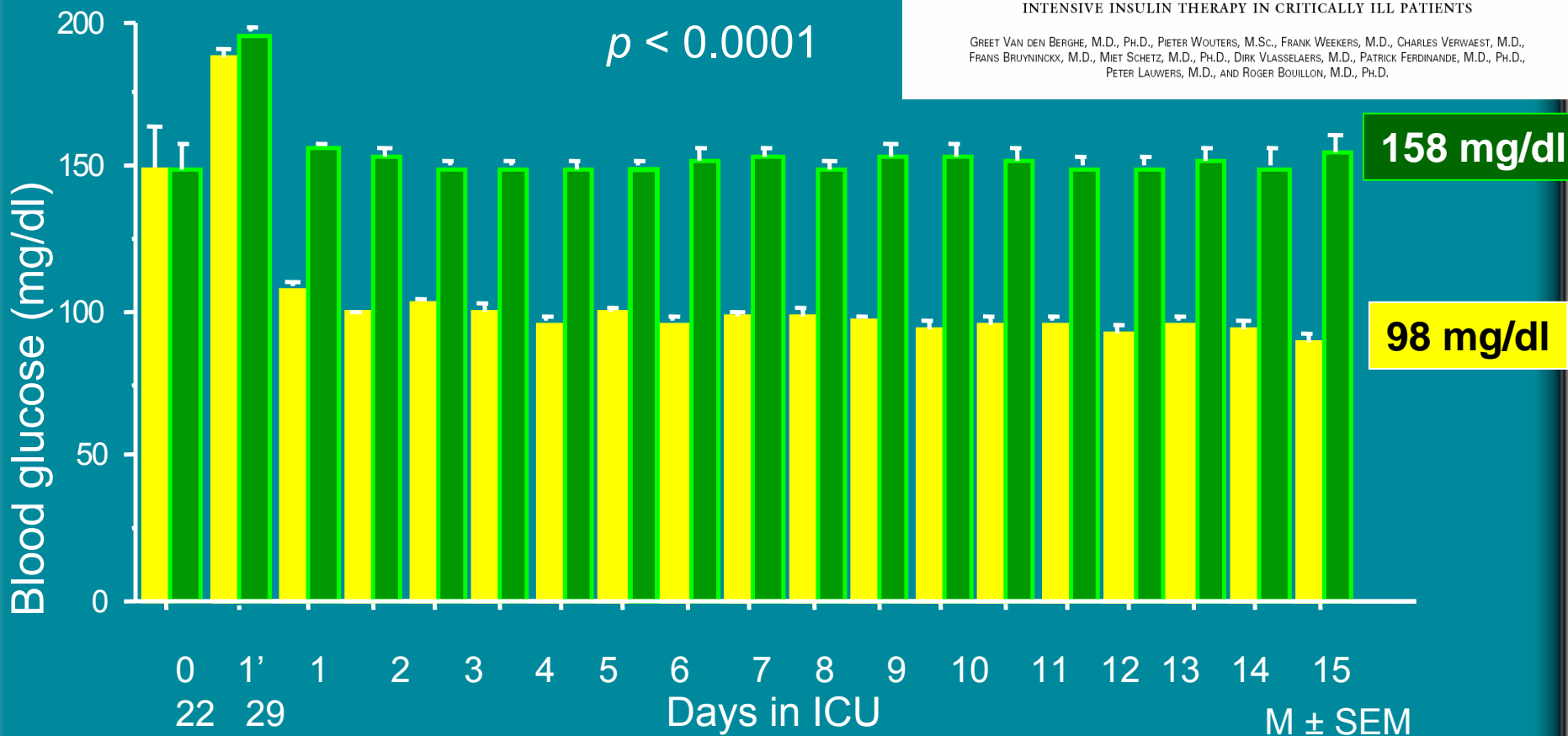
- What is the benefit ?
 - Results of the 2 Leuven RCTs (*surgical* and *medical* ICU)
 - Importance of achieving glycemic target !
- Conclusions

Blood glucose control



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 SCHEZT, M.D., PH.D., DIRK VLASSELAERS, M.D., PATRICK FERDINANDE, M.D., PH.D.,
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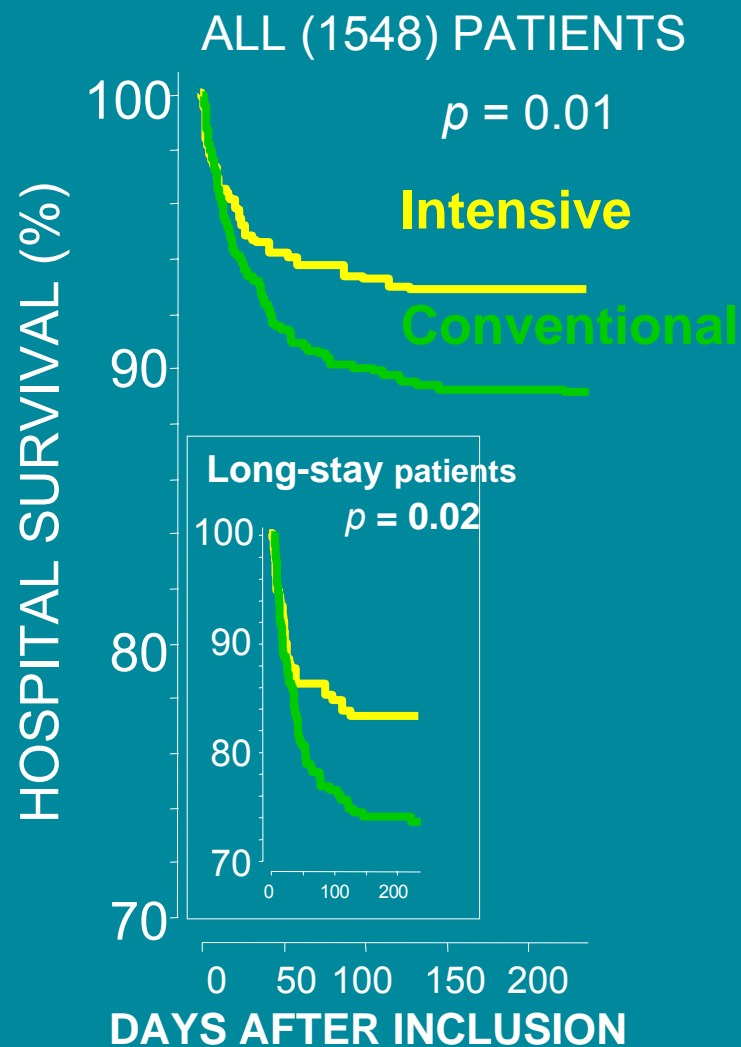
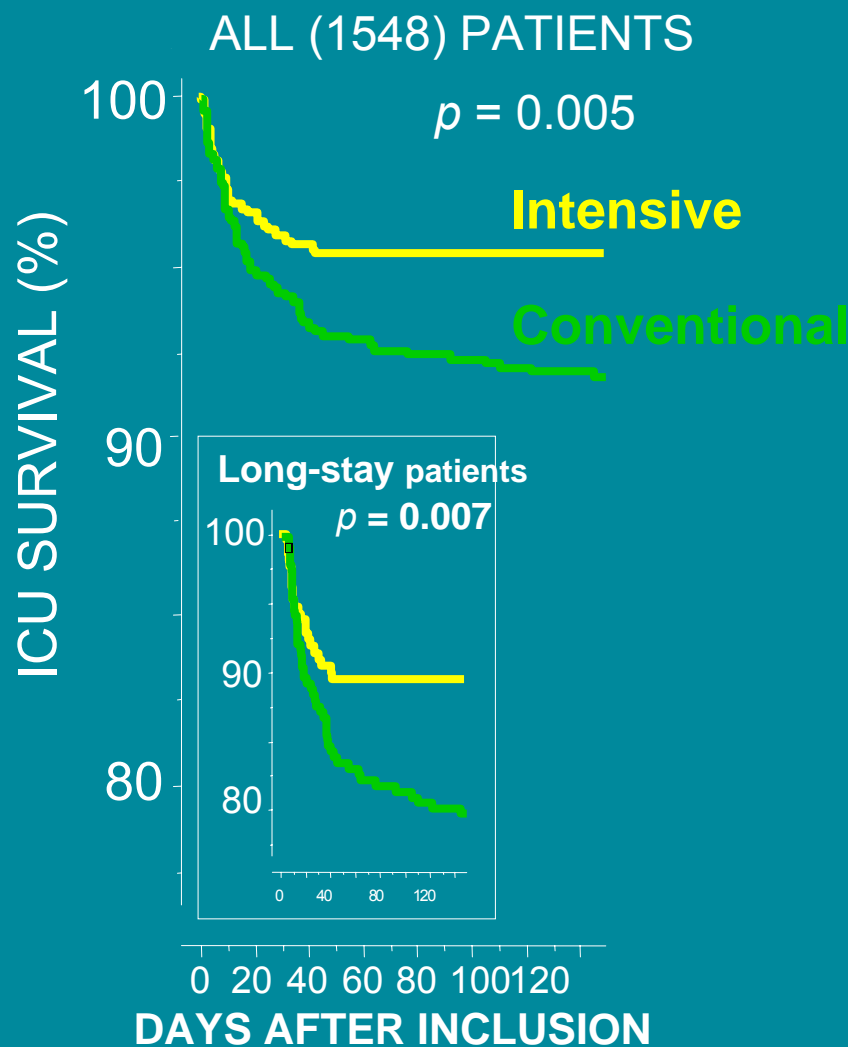


Van den Berghe G et al. *N Engl J Med* 2001

Van den Berghe G et al. *Crit Care Med* 2003

■ Conventional ■ Intensive

Mortality S-ICU study: Kaplan-Meier plots

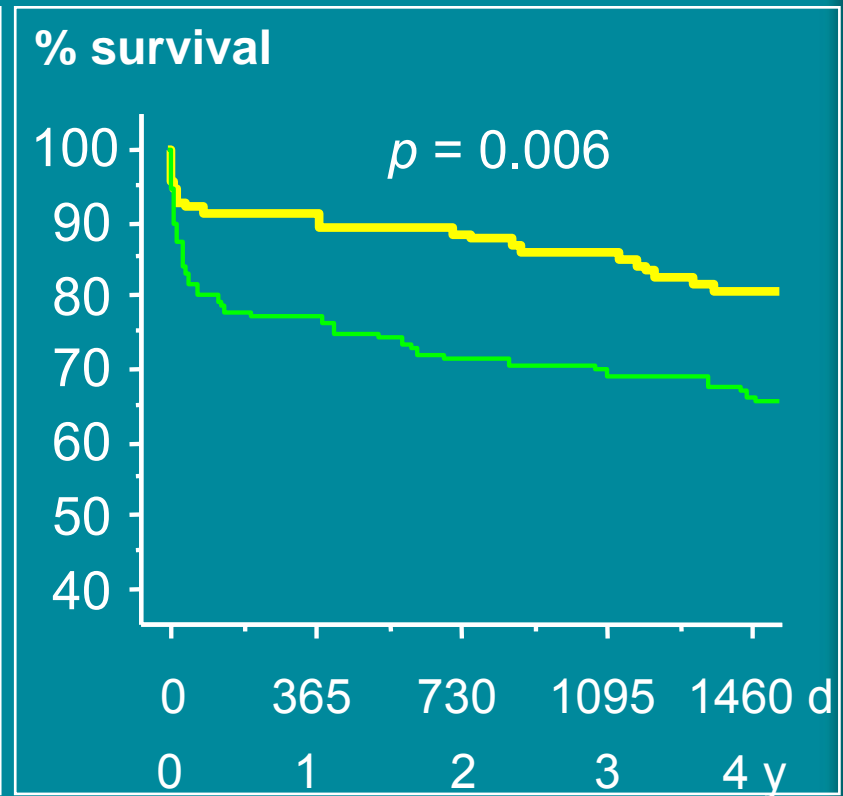


Van den Berghe G et al. N Engl J Med. 2001; 345: 1359-1367

Long-term (up to 4 y) outcome cardiac surgery pat. in ICU $\geq 3d$

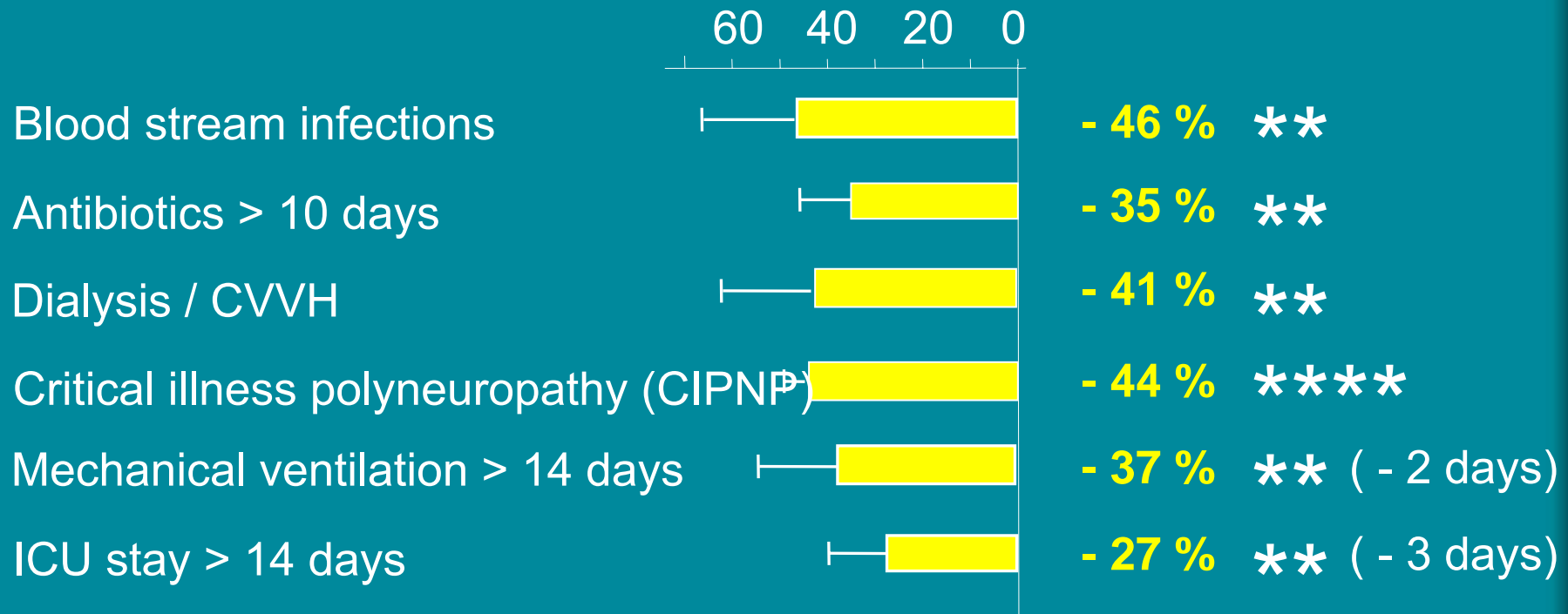
Ingels C. et al. *European Heart Journal* 2006, 27: 2716-2724

	Conventional	Intensive	<i>p</i>
EuroSCORE (M \pm SD)	8.0 \pm 4.1	7.6 \pm 4.3	NS
Euroscore-predicted †	17 %	15 %	NS
ICU - †	15 %	6 %	*
2 y - †	29 %	10 %	***
3 y - †	31 %	15 %	***
4 y - †	36 %	23 %	*



Morbidity in S-ICU study

Relative Risk Reduction (%)



** $p \leq 0.01$ **** $p < 0.0001$

Van den Berghe G et al. *N Engl J Med.* 2001; 345: 1359-1367

And ... it saved a median 2,638.00 € per patient

Parameter	Costs per patient (€) (median)	
	Intensive Therapy (n=765)	Conventional Therapy (n=783)
ICU stay	6,826.00	8,833.00
Mechanical Ventilation	204.00	283.00
Dialysis	196.00	473.00
Inotropic Support	52.00	70.00
Vasopressor Support	11.00	17.00
Antibiotic Treatment	270.00	438.00
Blood Transfusions	228.00	383.00
Insulin Administration / Blood Glucose Monitoring	144.00	72.00

PER PATIENT TOTAL

€7,931.00

€10,569.00

Van den Berghe G et al., Crit Care Med 2006, 34: 612-616

Surgical ICU

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Medical ICU ?

Mortality-benefit in S-ICU as function of duration of therapy

	N	hosp mortal	ARR	<i>p</i>
All	1548	10.9% --> 7.2%	-3.7%	0.01
At least 2d	851	16.2% --> 11.4%	-4.8%	0.04
At least 3d	622	20.6% --> 13.6%	-7.0%	0.02
At least 4d	518	23.5% --> 14.6%	-8.9%	0.01
At least 5d	451	26.3% --> 16.8%	-9.5%	0.01

Vanhorebeek I et al. Chest 2007 in press

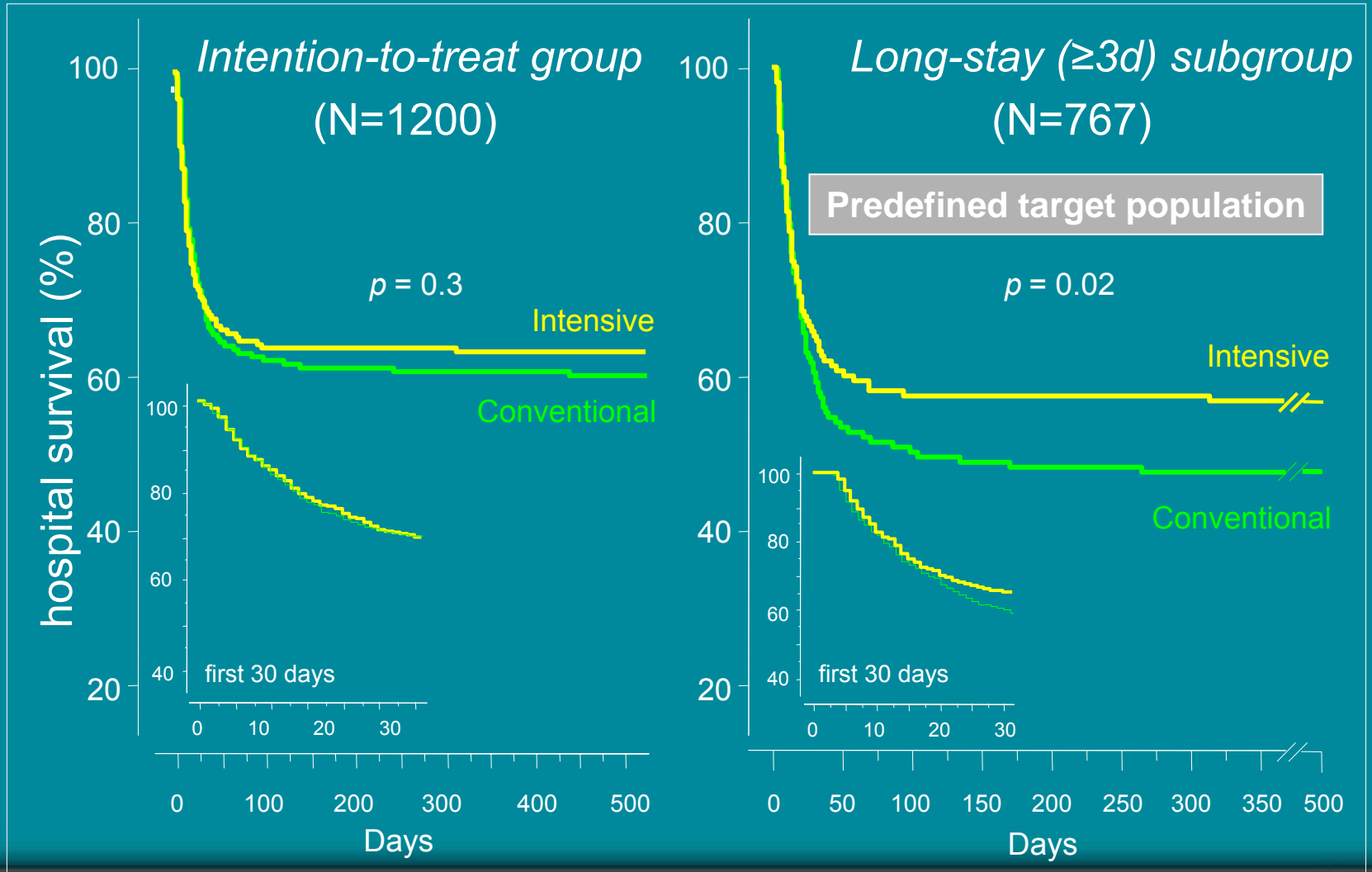
Study design and methodology : MICU study

N Engl J Med. 2006; 354: 449-461

- **Target population** : in ICU for **at least a third day** (based on SICU study results: at least 3 days required)
 - Difficult/impossible to predict stay in ICU !
 - **Power = 80%** and type I error = 0.05 : **for a 7% ARR among long-stay patients, need to include at least 1200 to achieve +/- 700 patients in ICU for at least a third day**
- **Study protocol** : similar to surgical study
- **Feeding** : As according to standing guidelines in the unit (enteral feeding as early as possible)

Results : mortality MICU study

N Engl J Med. 2006; 354: 449-461



Mortality-benefit in S-ICU & M-ICU for duration of therapy

	N	ARR S-ICU	p	N	ARR M-ICU	p
All	1548	-3.7%	0.01	1200	-2.7%	0.3
At least 2d	852	-4.8%	0.04	905	-8.0%	0.01
At least 3d	622	-7.0%	0.02	767	-9.5%	0.008
At least 4d	518	-8.9%	0.01	658	-8.5%	0.03
At least 5d	451	-9.5%	0.01	576	-9.0%	0.03

Vanhorebeek I et al. Chest 2007 in press

Mixed MICU / SICU population ?

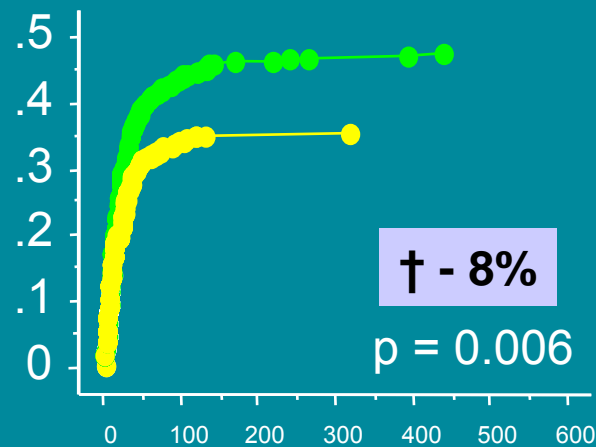
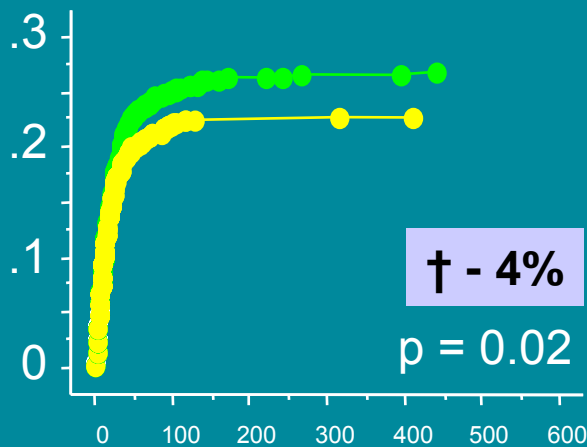
Mixed M-ICU / S-ICU population (N=2748)

Van den Berghe G et al. DIABETES 2006, 55: 3151-3159

Cumulative risk for in-hospital mortality

Intention-to-treat
(N = 2748)

In ICU at least 3 days
(N = 1389)



Hosp mort **24%** -> **20%**

Hosp mort **38%** -> **30%**

- Conventional
- Intensive

Subgroups ? (large enough to get an idea...at least N=400)

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	Conventional	Intensive
Cardiovascular (N)	549	533
New kidney injury	35 (6%)	17 (3%)
Critical Illness Polyneuropathy	41 (41%)	17 (23%)
Hospital mortality	48 (9%)	34 (6%)



Van den Berghe G et al. *DIABETES* 2006, 55: 3151-3159

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Critical Illness Polyneuropathy	41 (41%)	17 (23%)	
Hospital mortality	48 (9%)	34 (6%)	
Respiratory / thoracic (N)	317	317	
New kidney injury	36 (11%)	20 (6%)	↓
Critical Illness Polyneuropathy	71 (53%)	48 (35%)	
Hospital mortality	128 (40%)	103 (33%)	

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Critical Illness Polyneuropathy	71 (53%)	48 (35%)	
Hospital mortality	128 (40%)	103 (33%)	
Gastrointestinal or hepatic (N)	210	199	
New kidney injury	11 (5%)	7 (3%)	↓
Critical Illness Polyneuropathy	38 (51%)	18 (33%)	
Hospital mortality	60 (29%)	50 (25%)	

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Hospital mortality	60 (29%)	50 (25%)	
Sepsis (N)	471	479	
New kidney injury	49 (10%)	34 (7%)	↓
Critical Illness Polyneuropathy	114 (53%)	69 (32%)	
Hospital mortality	172 (37%)	160 (33%)	

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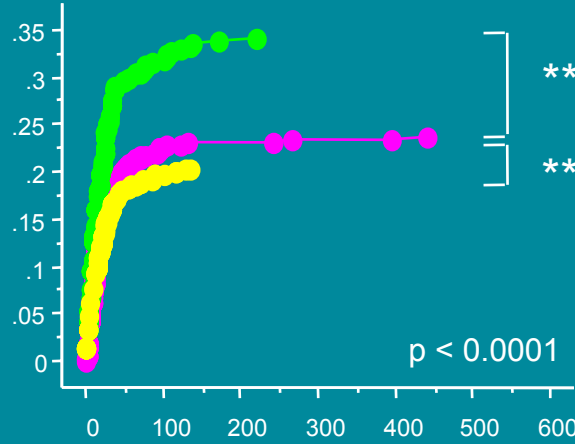
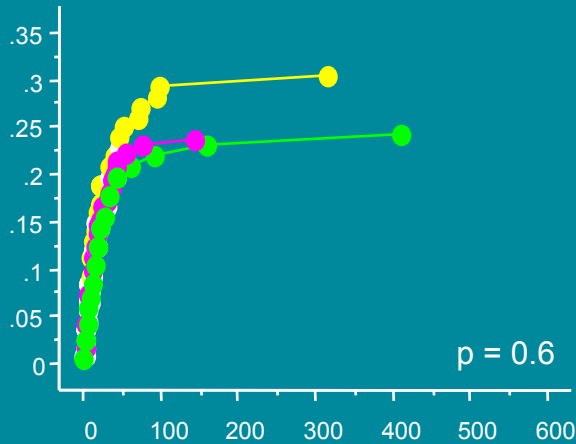
Conventional

Intensive

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New kidney injury	49 (10%)	34 (7%)	↓
Critical Illness Polyneuropathy	114 (53%)	69 (32%)	
Hospital mortality	172 (37%)	160 (33%)	
Diabetes (N)	200	207	
New kidney injury	14 (7%)	11 (5%)	?
Critical Illness Polyneuropathy	25 (44%)	14 (33%)	
Hospital mortality	44 (22%)	48 (23%)	

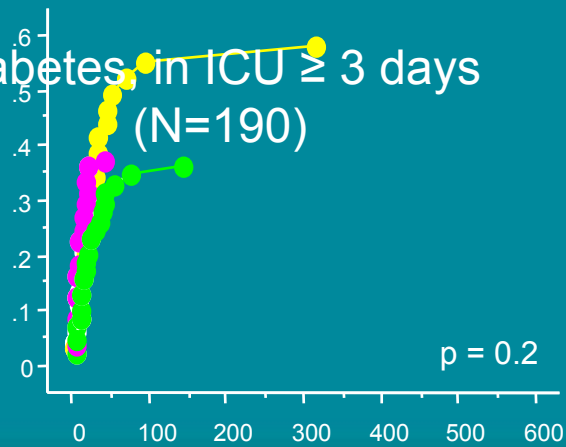
Patients with history of diabetes (N=407)?

Cumulative risk for in-hospital mortality
 diabetes (N=407) no diabetes (N=2341)

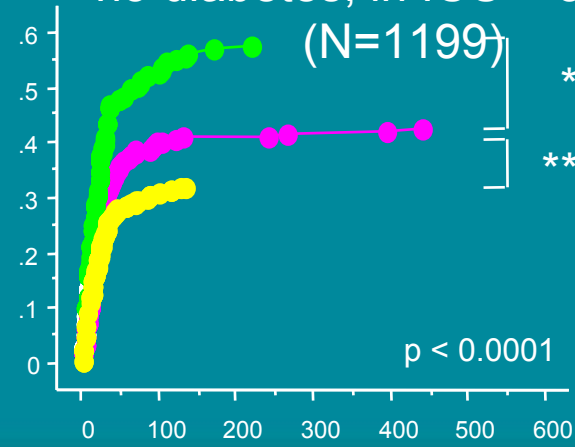


- mean BG > 150 mg/dl
- mean BG 110-150 mg/dl
- mean BG <110 mg/dl

diabetes, in ICU ≥ 3 days
 (N=190)



no diabetes, in ICU ≥ 3 days
 (N=1199)



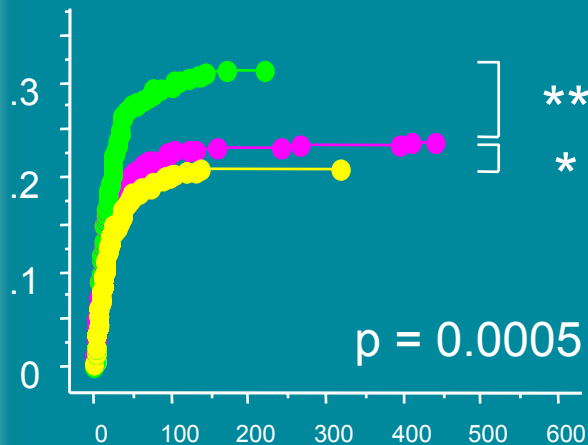
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Mixed M-ICU / S-ICU population (N=2748)

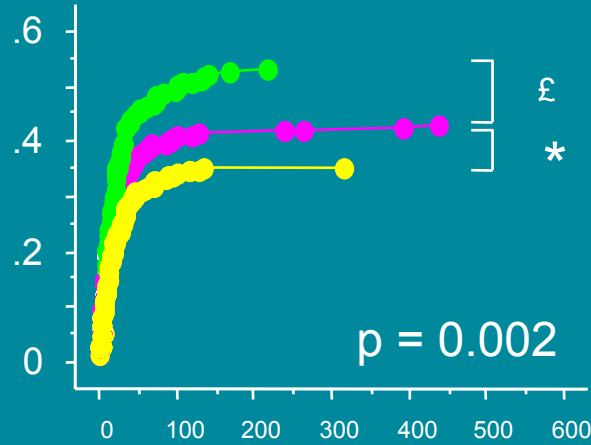
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Cumulative risk for in-hospital mortality

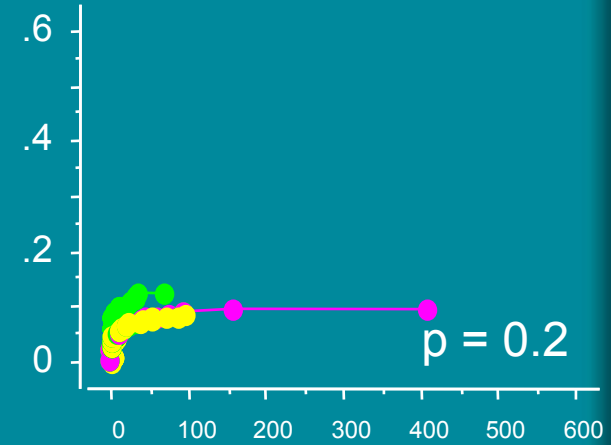
Intention-to-treat
(N = 2748)



In ICU at least 3 days
(N = 1389)



In ICU <3 days
(N = 1359)



- mean BG > 150 mg/dl
- mean BG 110-150 mg/dl
- mean BG < 110 mg/dl

days after inclusion

Overview : Intensive insulin (glucose control) therapy in critical illness

- What is the benefit ?
 - Results of the 2 Leuven RCTs (*surgical* and *medical* ICU)
 - Importance of achieving glycemic target !
- Conclusions

Blood glucose control



Conventional

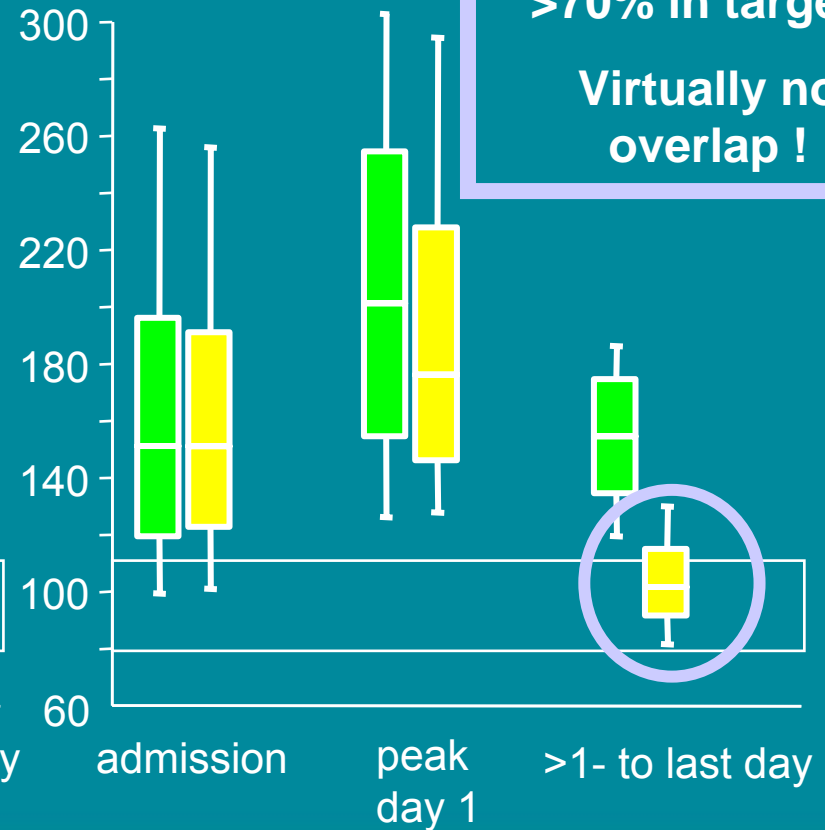
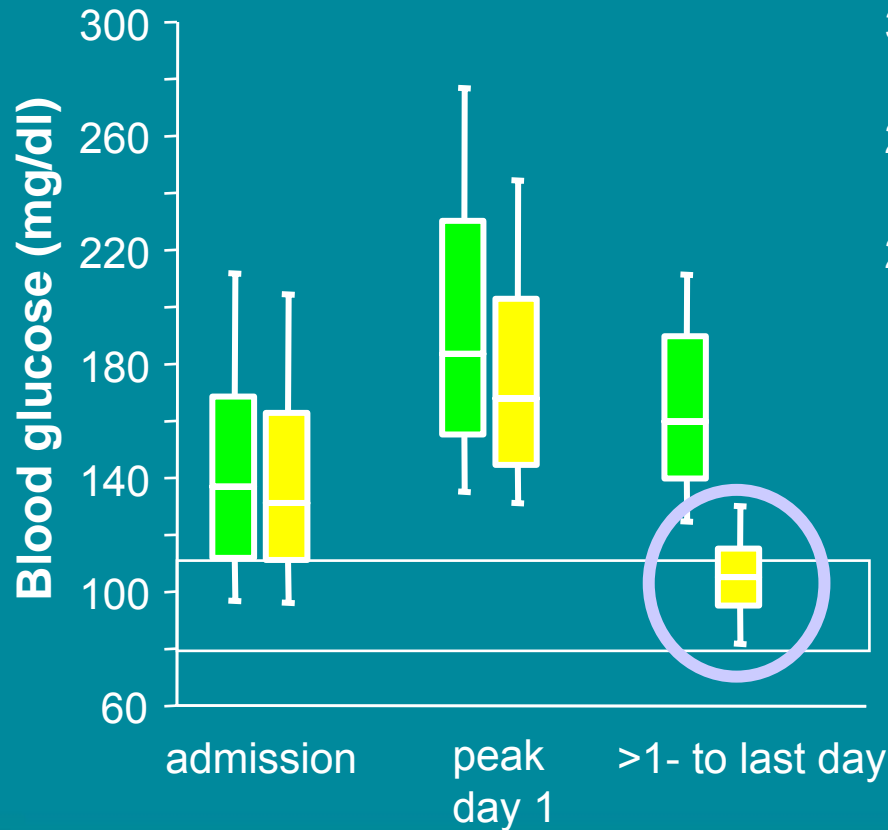


Intensive

S-ICU

M-ICU

N Engl J Med. 2001 & 2006



>70% in target !
Virtually no overlap !

Conclusions : what's the evidence for IIT in SICU/MICU?

- 2 large RC single center studies : **Strict** maintenance of normal BG levels (**target <110 mg/dl**) with insulin **for at least 3 days**, reduces morbidity and mortality of **all** ICU patients, without causing harm (*exclusive known diabetics with long-standing hyperglycemia??*)
- Avoiding **glucose toxicity** whereby **mitochondrial damage** has a beneficial impact on **multiple organ systems**
- Reaching the **blood glucose target <110 mg/dl** is crucial, so, studies that do not achieve the target in the majority of the patients are invalid to test the hypothesis (*target for known diabetics with long-standing hyperglycemia may be higher??*)
- Avoid **hypoglycemia** (continuous BG sensors !)

ESC/EASD Pocket Guidelines

Diabetes, prediabetes and cardiovascular disease

Intensive care

Recommendation	Class	Level
Strict blood glucose control with intensive insulin therapy improves mortality and morbidity of adult cardiac surgery patients.	I	B
Strict blood glucose control with intensive insulin therapy improves mortality and morbidity of adult critically ill patients.	I	A

ESC/EASD Pocket Guidelines

Diabetes, prediabetes and cardiovascular disease

Published trials on intensive insulin therapy in intensive care

Patient population ^a	Surgical	Medical	Surgical and medical	Surgical	Heart surgery in diabetes
Number of patients	1548	1200/767 ^b	1600	61	4864
Randomized study	Yes	Yes	No	Yes	No
Target glucose (mmol/L)	< 6.1	< 6.1	< 7.8	< 6.7	< 8.3
Mortality-	ú	ú	ú		ú
Critical illness polyneuropathy	ú				
Bacteraemia/ severe infections	ú	-	-	ú	
Acute renal failure	ú	ú	ú		
Red blood cell transfusions	ú		ú		
Duration of mechanical ventilation	ú	ú			
Length of stay	ú	ú	ú		ú
Deep sternal wound infections					ú