Oral melatonin decreases need for sedatives and analgesics in critically ill

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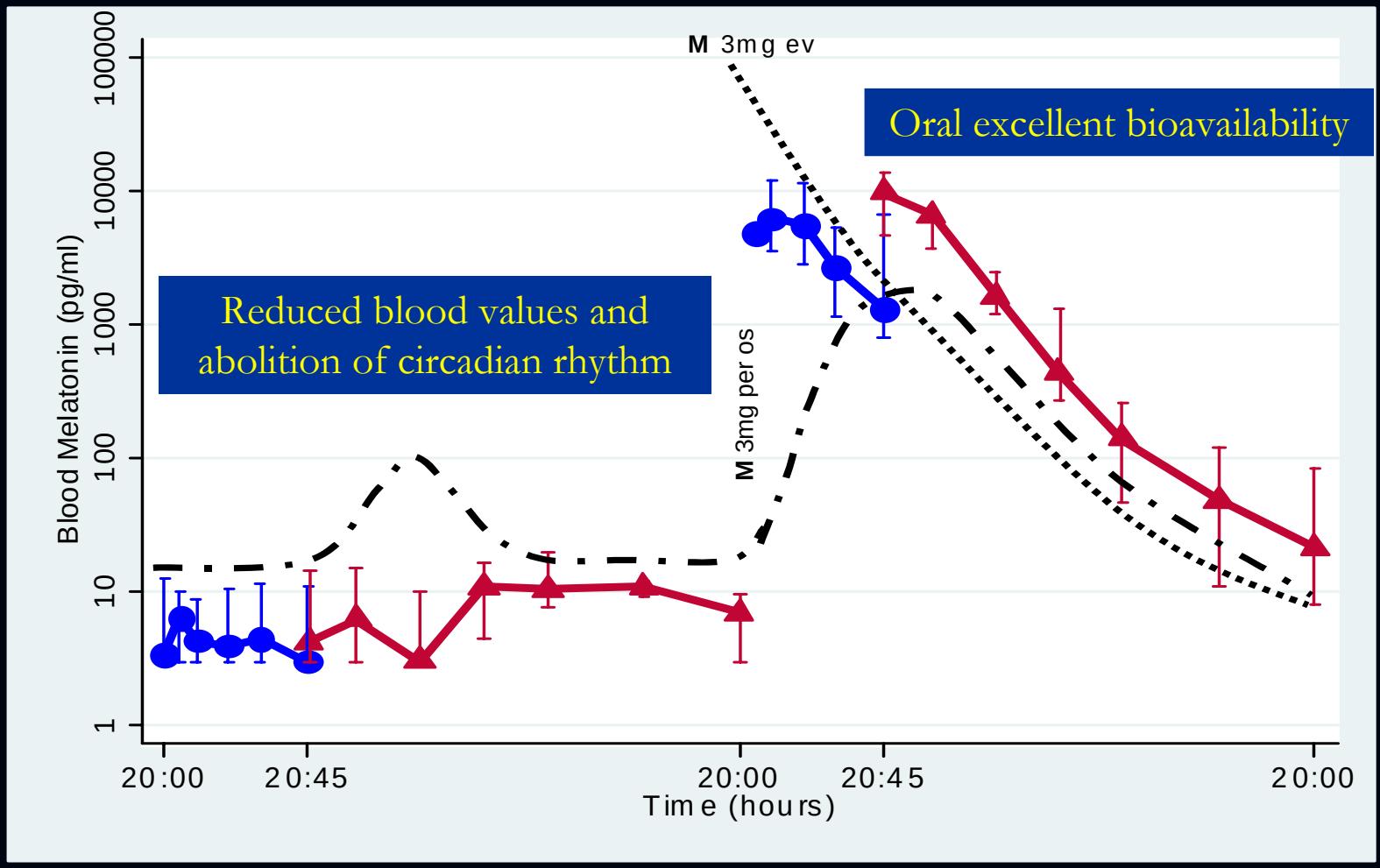
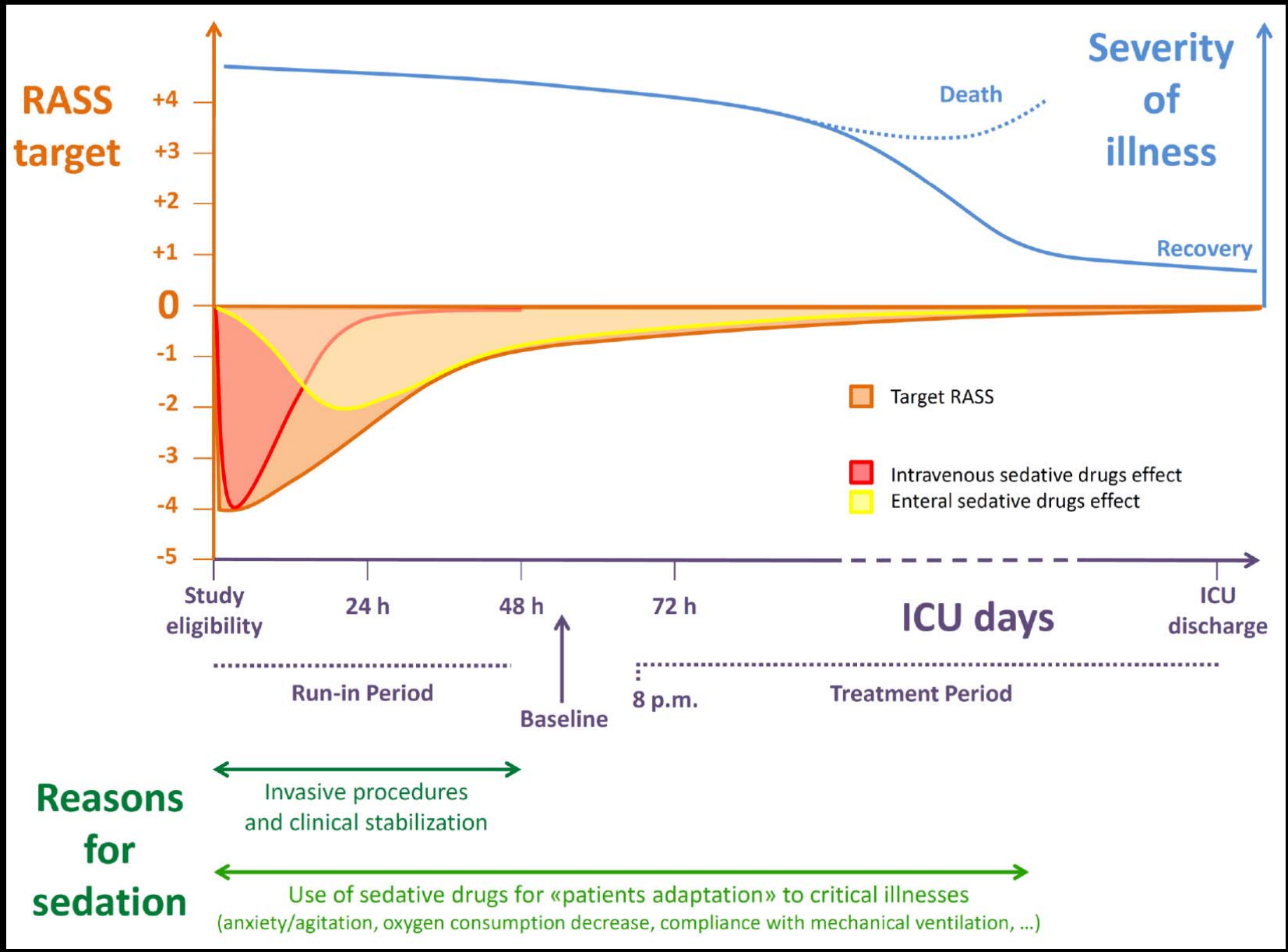
Background

Melatonin pharmacokinetiks in high risk critically ill

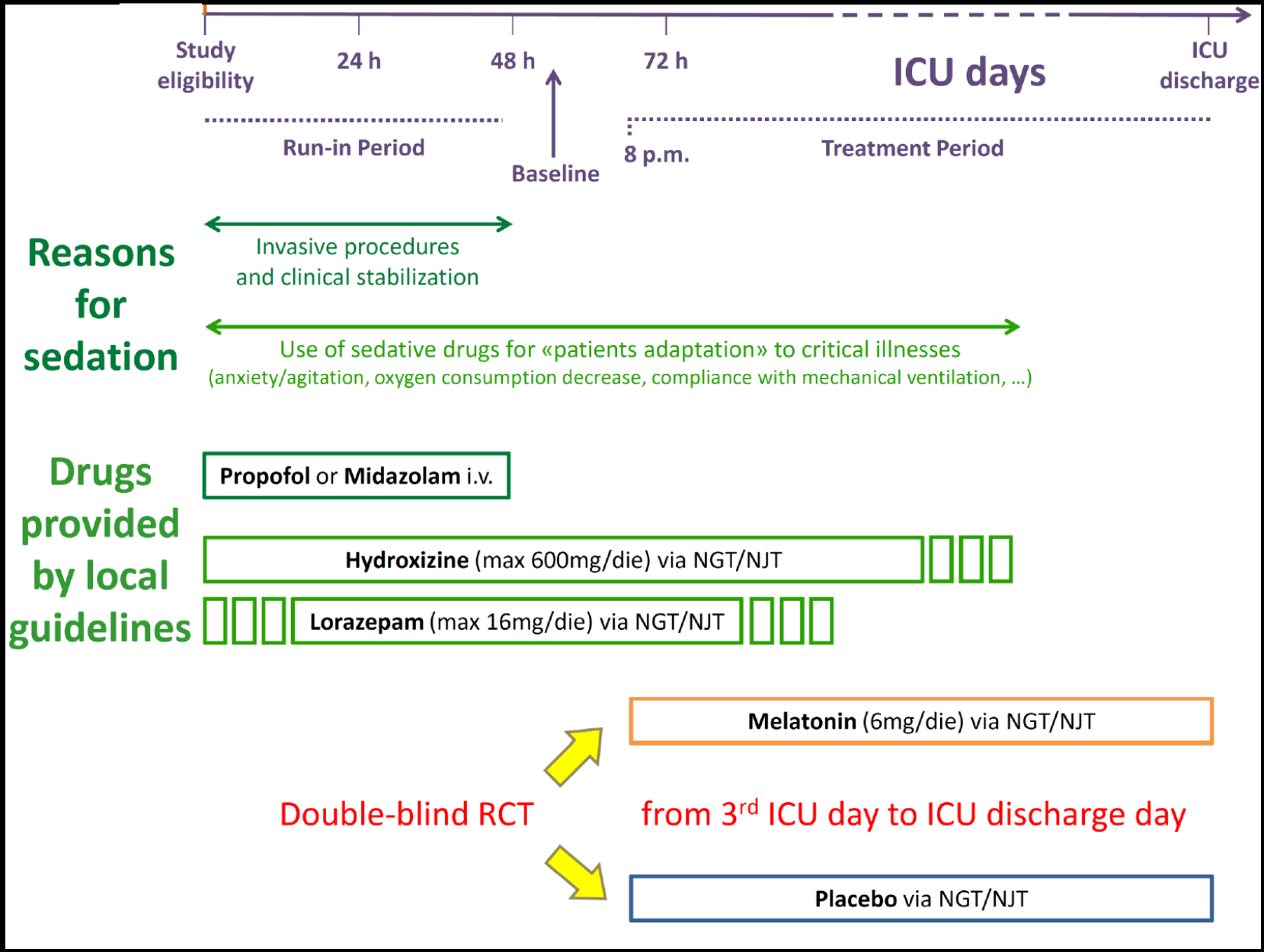


Mistraletti G, J Pinel Res, 2010

Materials and methods



Materials and methods - 2



Aims of the study
(ClinicalTrials.gov Identifier: NCT00470821)

Primary Outcome Measure

* Overall sedatives and analgesics daily doses

Secondary Outcome Measures:

* Neurological indicators (pain, anxiety, agitation, delirium, need for restraints, need for extra drugs)
* Prevalence of mental disorders
* ICU length of stay
* ICU and hospital mortality
* Sleep quantity
* Cost for sedatives and analgesics

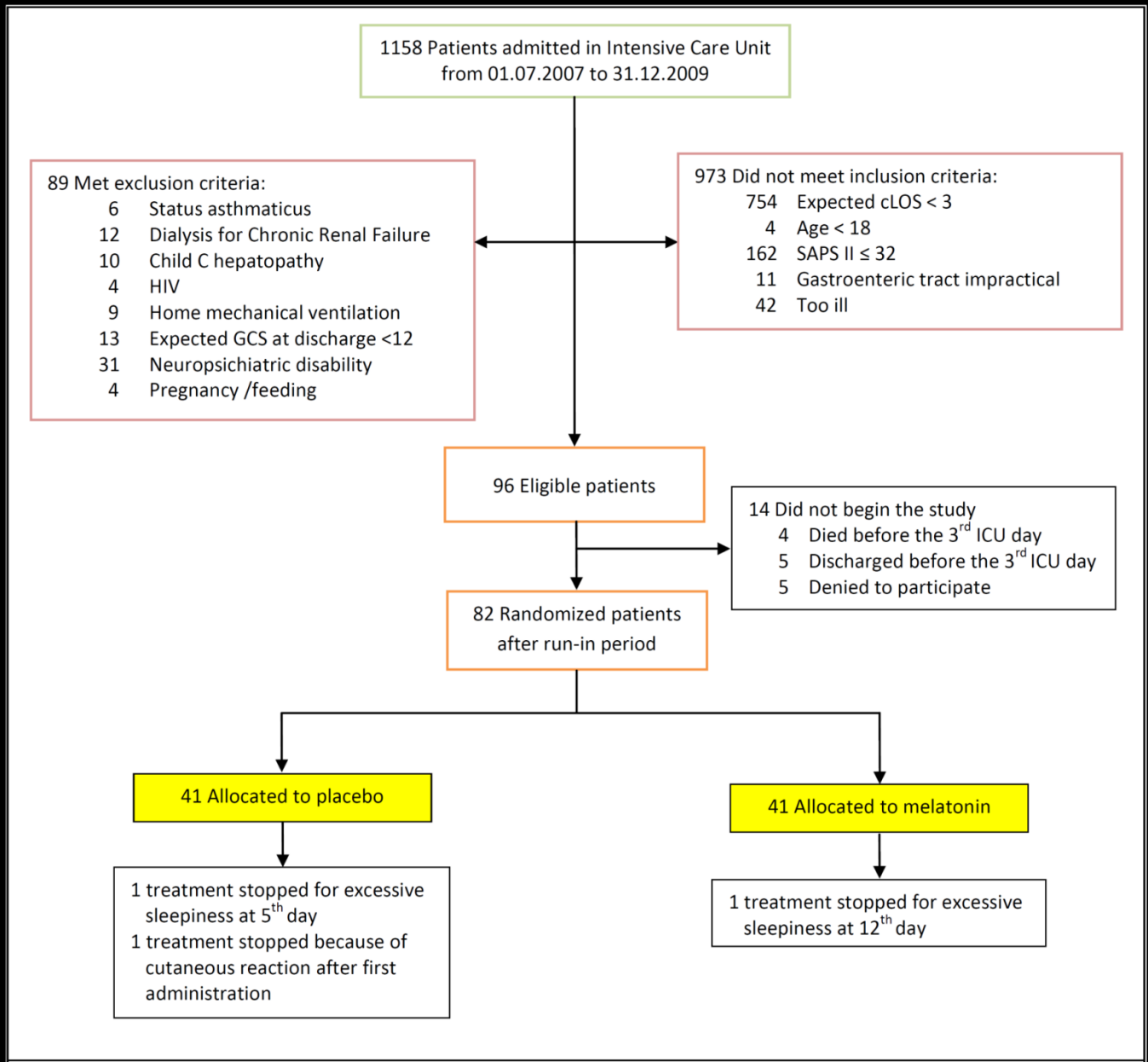


Figure 1. Screening and randomization process.
The 82 randomized patients were analyzed with intention to treat approach, without considering the treatment interruptions. HIV denotes Human Immunodeficiency Virus, GCS Glasgow Coma Scale, cLOS Critical Length of Stay, SAPS Simplified Acute Physiology Score, ICU Intensive Care Unit.

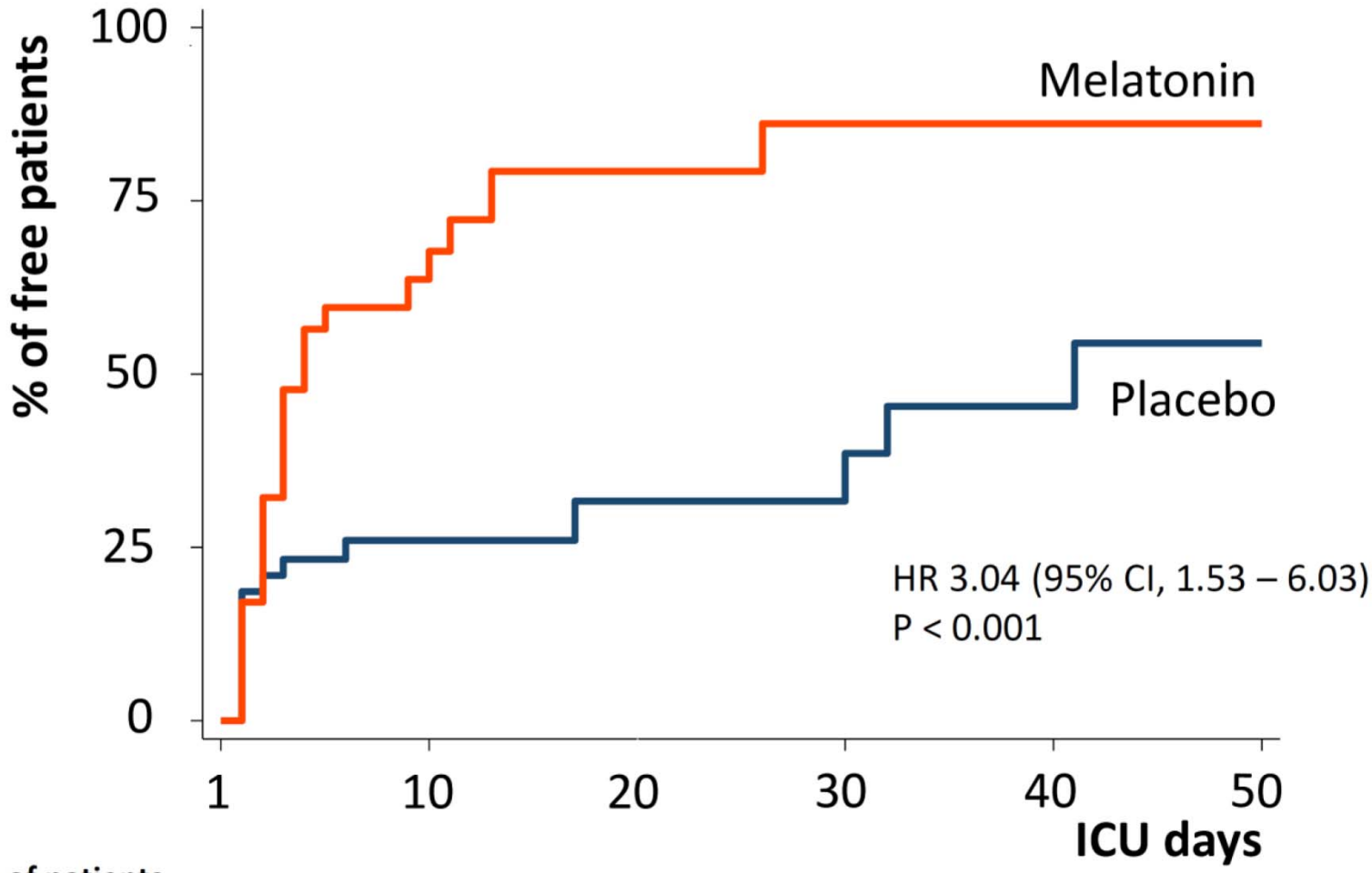
Case-mix

Variables	Placebo (n=48)	Melatonin (n=48)	p
Age (Years)	64.2 ± 15.5	67.6 ± 14.8	0.273
Sex: n male (%)	34 (70.8)	27 (56.3)	0.203
SAPS II (points)	43.1 ± 15.5	44.4 ± 17.4	0.698
Admission type: n (%)			
medical	31 (64.6)	32 (66.7)	0.903
Surgical scheduled	13 (27.1)	11 (22.9)	
Surgical unscheduled	4 (8.3)	9 (9.4)	
DIAGNOSIS: n (%)			
Pancreatic diseases	9 (18.8)	8 (16.7)	0.950
Pneumonia – lung diseases	17 (35.4)	20 (41.6)	
Acute myocardial infarction	4 (8.3)	5 (10.4)	
Gastro intestinal diseases	3 (6.3)	4 (8.3)	
Cardiocirculatory arrest – arrhytmia	8 (16.7)	6 (12.5)	
Trauma	3 (6.3)	1 (2.1)	
Others	4 (8.3)	4 (8.3)	

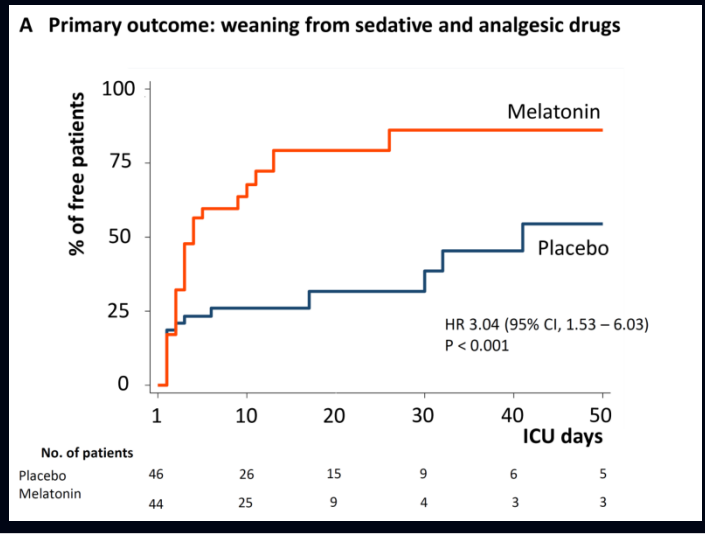
Main outcome

	Placebo = 41	Melatonin = 41	P
Hydroxizine p.o. (mg)	**2700** [100-8050]	**300** [0-2100]	**< 0.01**
Lorazepam p.o. (mg)	**1** [0-84]	**0** [0-8]	**< 0.01**
Haloperidol p.o. (mg)	**0** [0-15.9]	**0** [0-3]	**< 0.01**
Propofol i.v. (mg)	**20** [0-980]	**0** [0-40]	**< 0.01**
Midazolam i.v. (mg)	**0** [0-21]	**0** [0-0]	**< 0.01**
Morphine equivalents i.v. (mg)	**2.5** [0-82.5]	**0** [0-20]	**< 0.01**

A Primary outcome: weaning from sedative and analgesic drugs

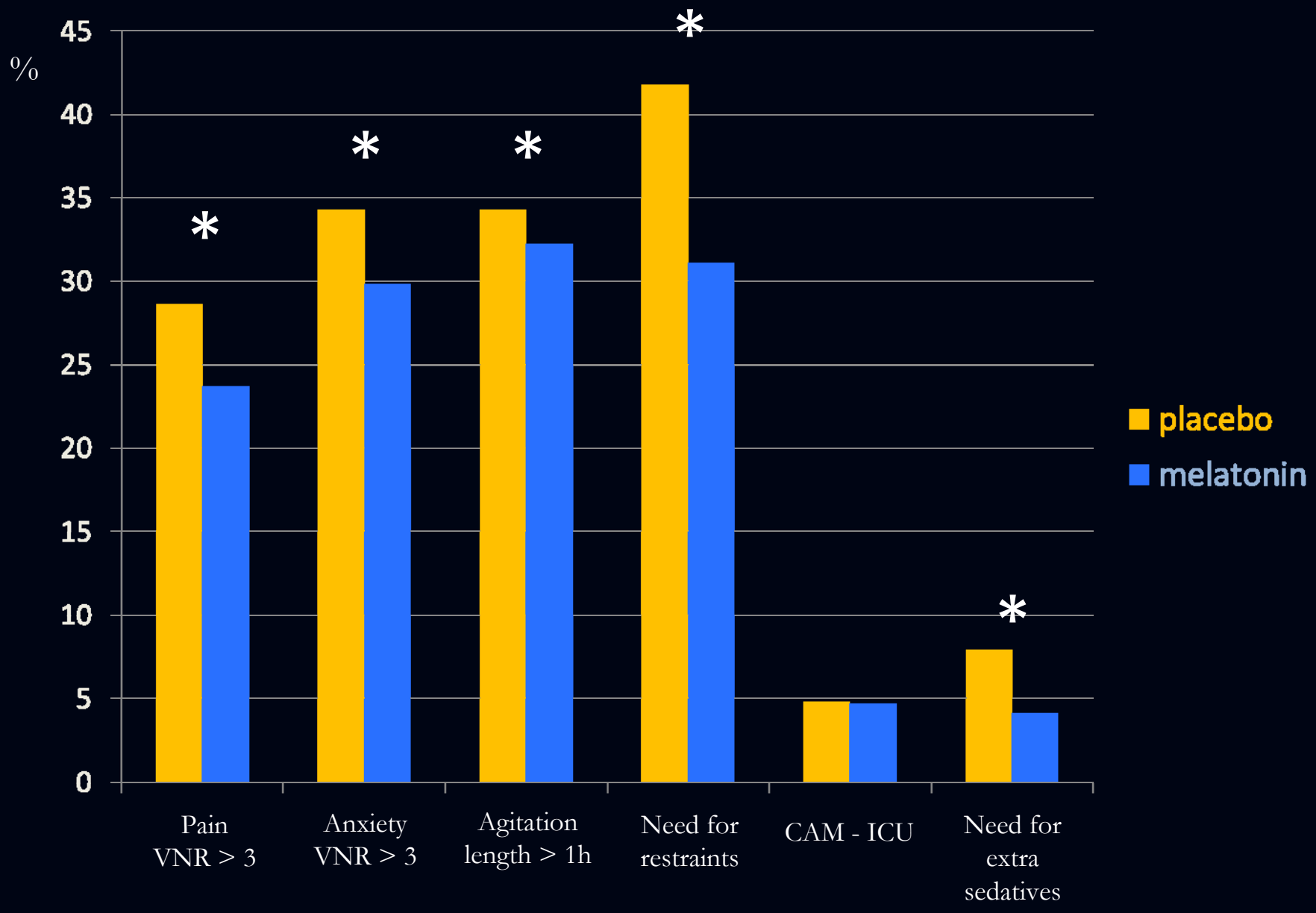


No. of patients						
Placebo	46	26	15	9	6	5
Melatonin	44	25	9	4	3	3

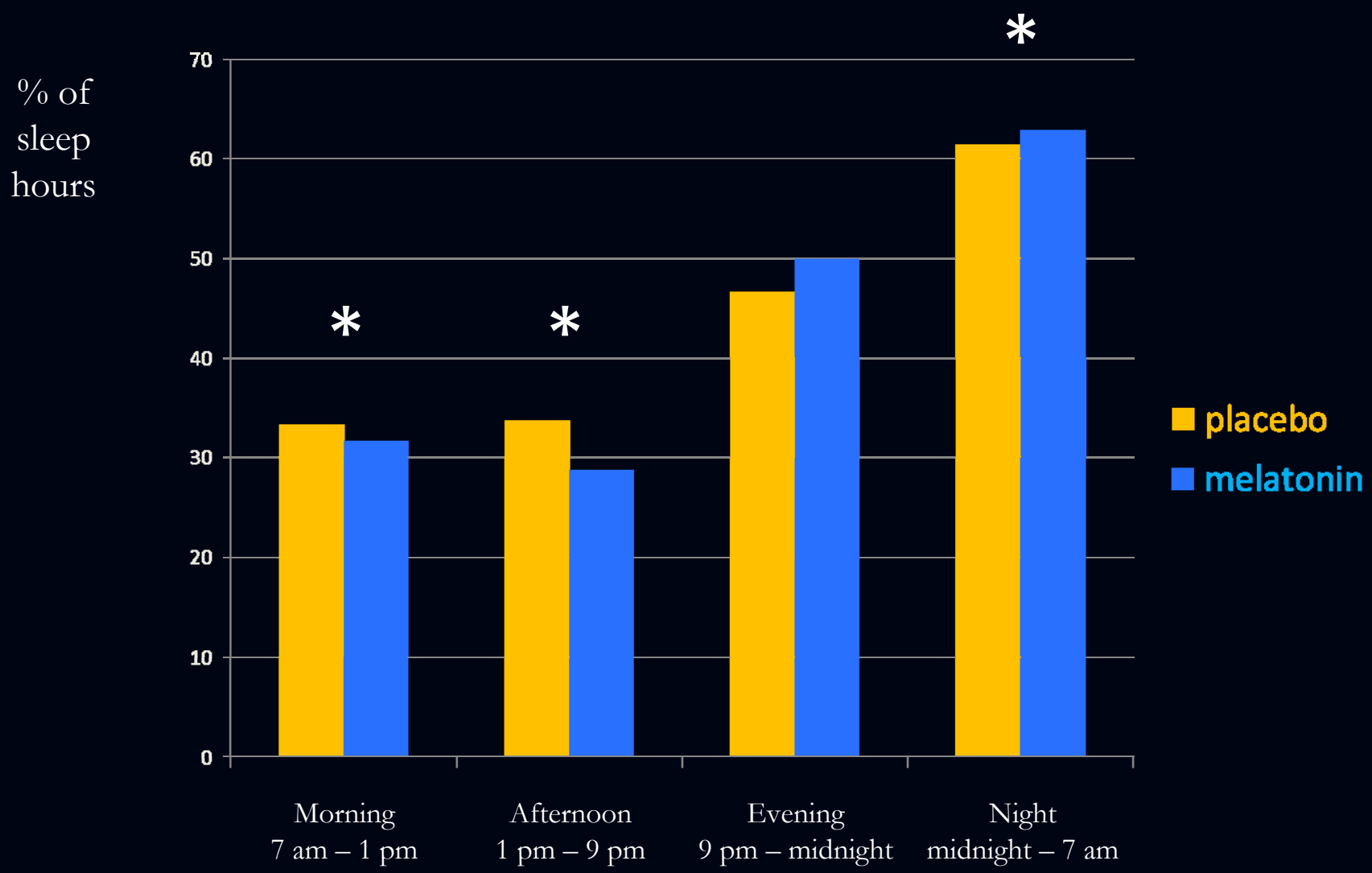


	Placebo 829 pts / day	**Melatonin** 602 pts / day	P
RASS (point)	0 [-1 – 0]	0 [0 – 0]	< 0.01
Adequacy of sedative therapy – no. (%)			
Insufficient	62 (14.6)	22 (6.8)	0.33
Adequate	353 (83.1)	298 (91.4)	
Excessive	10 (2.4)	6 (1.8)	
Type of sedation – no. (%)			
Entreral	599 (78.6)	435 (86.5)	< 0.01
Intravenous or mixed	163 (21.4)	68 (13.5)	

Secondary outcomes – neurological indicators



Secondary outcomes – Sleep



Secondary outcomes – Clinical outcomes

	Placebo	**Melatonin**	
Length of stay — days			
In ICU	12 [9-29]	15 [9-21]	*0.99*
High treatment	12 [6-29]	11 [7-18]	*0.67*
Low treatment	1 [0-3]	2 [0-5]	*0.21*
Mortality — no. (%)			
In ICU	14 (34.1)	10 (24.4)	*0.47*
In hospital	15 (36.6)	14 (34.1)	*0.82*
Psychiatric evaluation — no. (%)			
Delirium (CAM-ICU ⊕ at least once)	13/41 (31.7)	13/41(31.7)	*>0.99*
Patients examinated at ICU discharge	8/27 (29.6)	12/31 (38.7)	*0.58*
Psychiatric disease at discharge	5/8 (62.5)	5/12 (41.7)	*0.65*
Patients examinated 2 months after dicharge	5/8 (62.5)	9/12 (75.0)	*0.64*
Diagnosis of Post Traumatic Stress Disorder	0/5 (0)	2/9 (22.2)	*0.50*
Costs for drugs — €			
Total per patient	21.27 [1.23-69.50]	5.64 [2.15-13.75]	*<0.01*
Per ventilation day	1.59 [0.25-3.12]	0.50 [0.23-1.24]	*<0.01*

Conclusions

Long term administration of oral melatonin:

- is safe (no side effects, no excessive sleepiness);
- reduce need for analgesic and sedative drugs;
- show better neurological status indicators and improve cyrcadian rhythm;
- halves costs for analgesic and sedative drugs.

Those results, coming from a double-blind, single center RCT, need to be confirmed in a **large and multicentric RCT**.

«A new frontier in critical care: saving the injured brain»

E. W. Ely, 2010

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Materials and methods