Supplementary Online Content

van den Boogaard M, Slooter AJC, Brüggemann RJM. Effect of haloperidol on survival among critically ill adults with a high risk of delirium: the REDUCE randomized clinical trial. *JAMA*. doi:10.1001/jama.2018.0160

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eMethods 1. Definition of study objectives

Objective	Definition
Survival days in 28-days and 90-days	Number of days that patients survived in 28-day and 90-day after inclusion. All patients will be classified as either 'alive at study day 28, and 90' or, if dead, 'dead at study day 28 and 90' on an intention to treat basis
Delirium diagnosis	Patients were diagnosed as delirious when they have at least one positive CAM-ICU or ICDSC screening during their complete ICU stay. Patients who were not delirious during their ICU-stay were considered as non-delirious patients.
Delirium-and-coma-free days in 28-days	Number of days that the patient was alive and not delirious and not in coma in 28 days starting from the day of inclusion. A delirium-and-coma-free day is defined as a negative CAM-ICU or ICDSC screening with a Richmond Agitation Sedation Score (RASS) greater than (more alert than) -3/-4/-5 during a day. In case a delirious patient was discharged to the ward, a delirium-free day was defined as a delirium observation scale (DOS) score [24] of less than 3 during a complete day.
Duration of mechanical ventilation	Time in days that the patient was on the mechanical ventilator. If the patient was ventilated mechanically several times, then the ventilator times were added. Both invasive and non-invasive ventilation were registered.
Incidence of re-intubation	Patients who needed re-intubation within 28 days from inclusion, following a previous extubation, irrespectively the reason for re-intubation, were counted as incident case for re-intubation
Incidence of ICU readmission	Patients who were readmitted to the ICU within 28 days from inclusion, irrespectively the reason for readmission, were counted as incident cases for ICU readmission
Side effects	Drowsiness, agitation, QTc-time prolongation (using 12-leads ECG or monitor strip with Bazett's formula) and development of extra pyramidal symptoms: – dystonia - tremor- myoclonus – tics – rigidity – akathisia [26], determined daily by physical examination by the intensivist
Serious Adverse Event	Any untoward medical occurrence or effect at any dose that resulted in one of the following outcomes and were not classified as a clinical outcome of delirium or the underlying disease using the description above: - death that was not related to the underlying disease or sequel of the underlying disease, or death that was considered by the investigator to be possibly related to study drug - prolonged inpatient hospitalization or rehospitalisation - a life-threatening experience (immediate risk of dying) - persistent or significant disability/ incapacity - congenital anomaly/birth defect - considered significant by the investigator for any other reason

Suspected Unexpected Serious Adverse Reactions	Unexpected adverse reactions were adverse reactions, of which the nature, or severity, is not consistent with the applicable product information. Adverse reactions were all untoward and unintended responses to an investigational product related to any dose administered

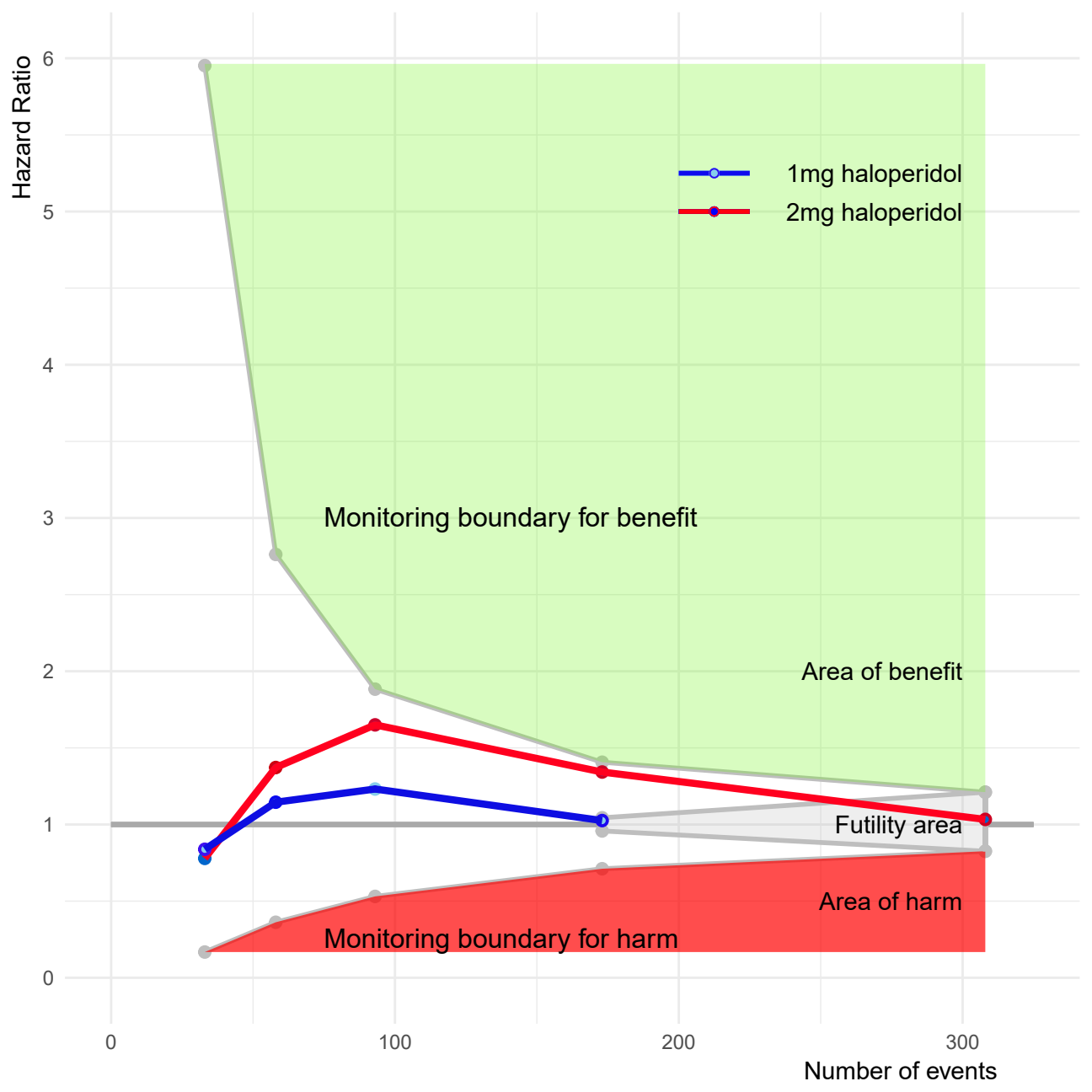
eMethods 2. The use of non-pharmacologic delirium preventive interventions in the participating centers.

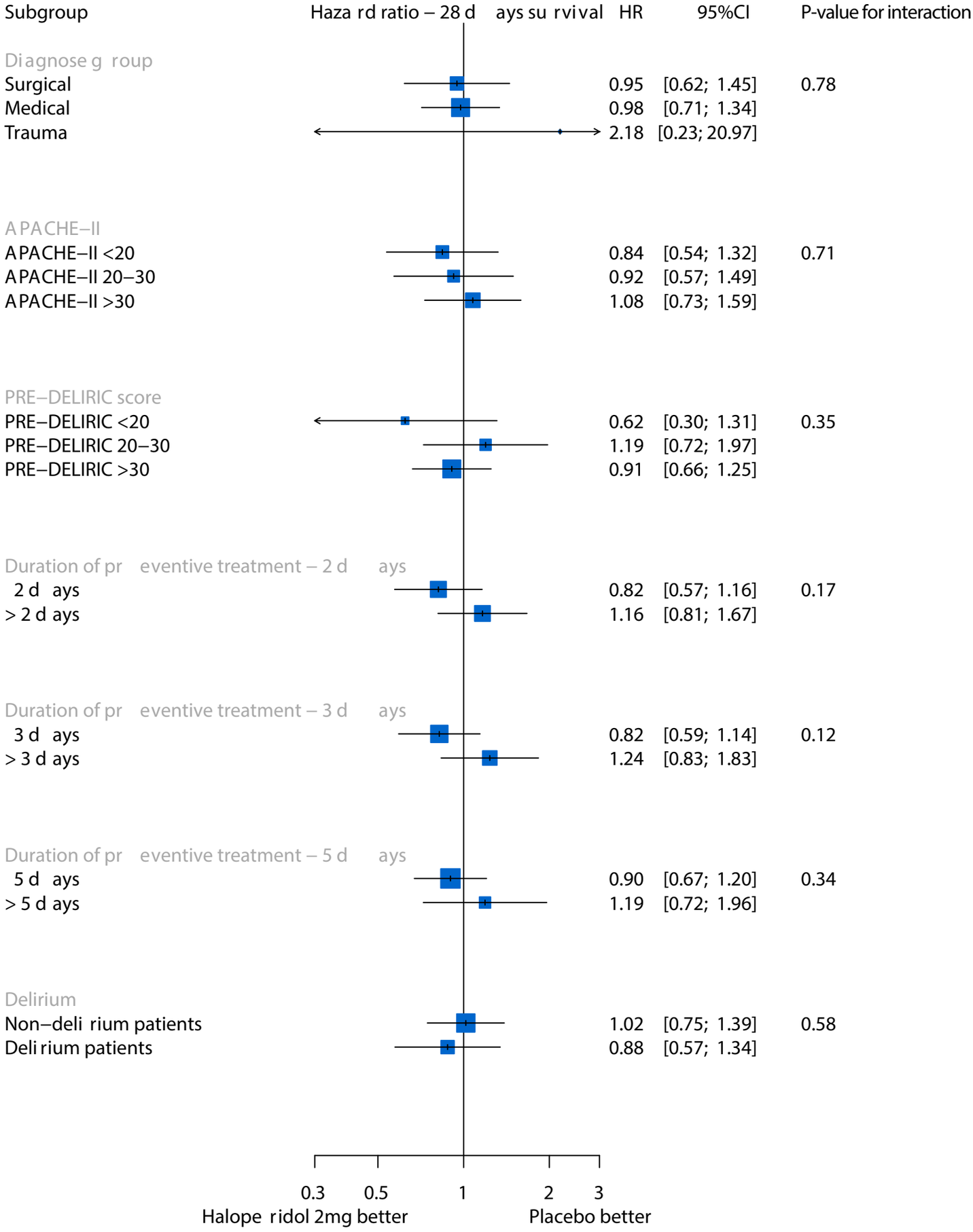
	Amphia hospital	Canisius Wilhelmina Hospital	Diakonessenhuis Utrecht	Gelre hospital	Haga hospital	ISALA	Jeroen Bosch Hospital	Haaglanden Medical Center Antonishove	Haaglanden Medical Center Bronovo	Haaglanden Medical Center Westeinde	Medical Centre Leeuwarden	MMC Veldhoven	Medical Spectrum Twente	Onze Lieve Vrouwe Gasthuis	Radboud umc	Scheper hospital	St Jansdal Harderwijk	UMC Groningen	UMC Utrecht	VieCuri Medical Center	Zuyderland Medical Center	**Overall applied (%)**
Early mobilization	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100%
Improving patient circadian rhythm (including sleep improvement protocol)	Y	Y	N	Y	Y	N	N	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	N	71%
Noise reduction strategy	N	Y	Y	Y	Y	N	N	Y	Y	Y	N	N	N	Y	Y	Y	N	Y	Y	Y	N	67%
Sedation protocol with less sedation (RASS 0/-1)	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	90%
Sedation-awakening trial protocol	Y	Y	Y	Y*	Y	N	Y	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	n	Y	Y	95%
Reducing use of benzodiazepines	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	90%
Use of hearing and visual aids	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100%
																					Mean overall score	**88%**
Miscellaneous:……..	** Sedation targeted station strategy																					

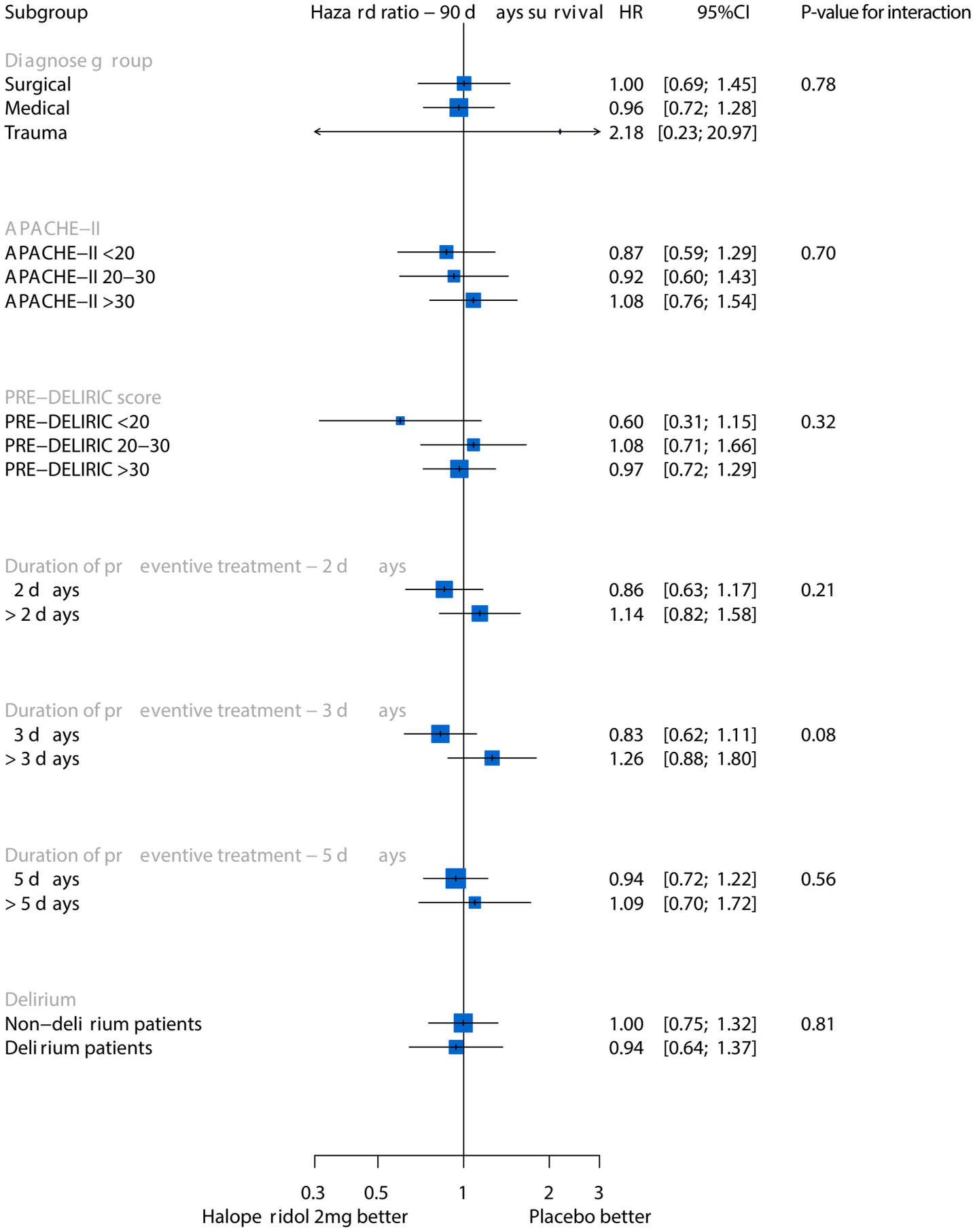
eTable 1. Primary and secondary outcomes **[per protocol analysis]**

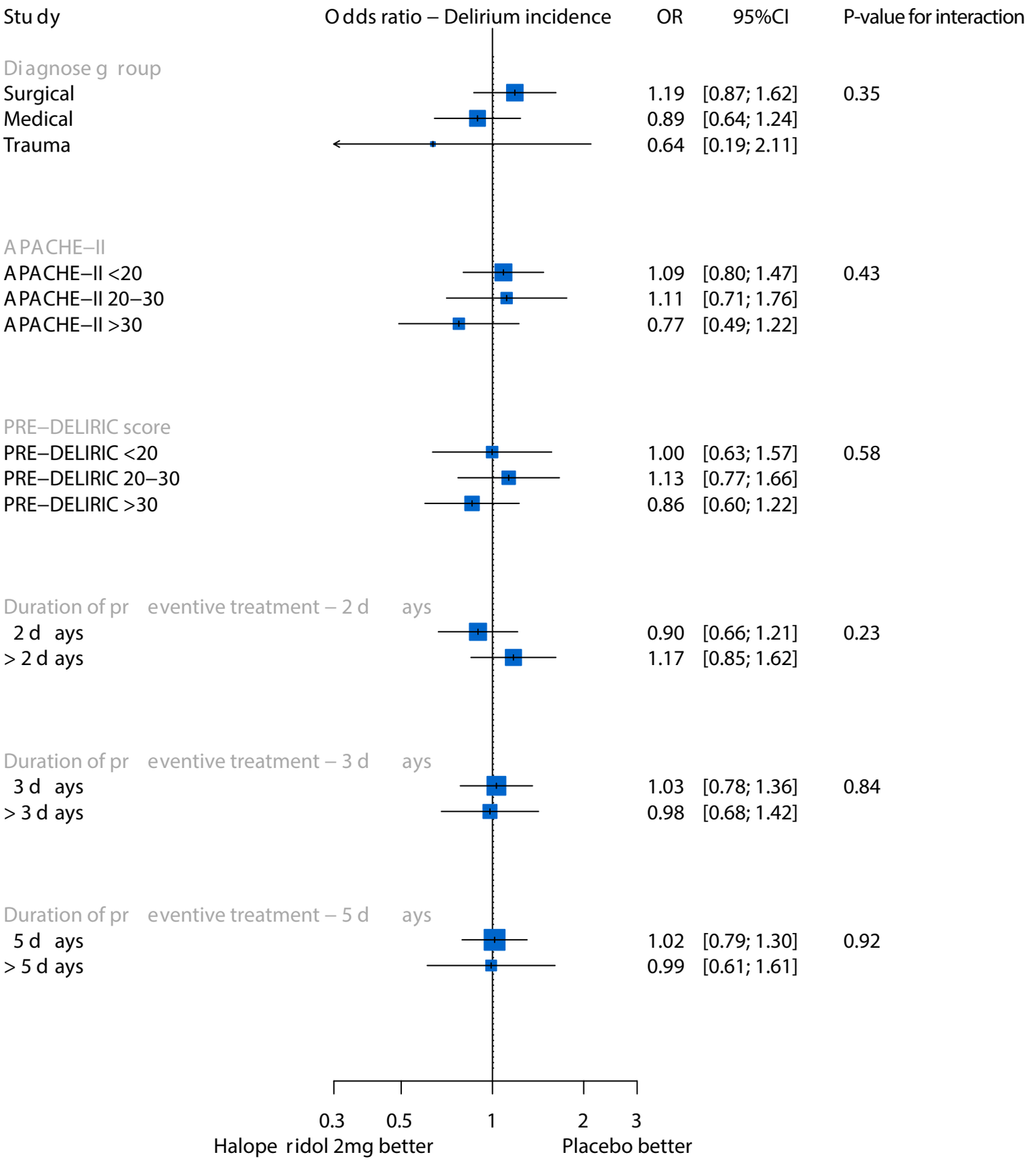
	2 mg haloperidol (N=682)	placebo (N=668)	*Difference (95%CI) 2 mg haloperidol - placebo*	1 mg haloperidol (N=331)
Survival in 28-days, n (%)	568 (83.3)	555 (83.1)	*0.2 (-3.9-4.3)*	270 (81.6)
Survival in 90-days, n (%)	540 (79.2)	527 (78.9)	*0.3 (-4.2-4.8)*	259 (78.2)
Delirium incidence, n (%)	233 (34.2)	218 (32.6)	*1.5 (-3.6-6.7)*	129 (39.0)
Number of delirium-coma-free days in 28-days, median [IQR]	26 (17-28)	26 (19-28)	*0.0 (0 to 0)***	26 (17-28)
Number of delirium-free days in 28-days, median [IQR]	28 (22-28)	28 (23-28)	*0.0 (0 to 0)***	28 (21-28)
Number of coma-free days in 28-days, median [IQR]	27 (22-28)	27 (23-28)	*0.0 (0 to 0)***	27 (21-28)
Number of days to occurrence delirium, median [IQR]	3 (2-6)	3 (2-6)	*0.0 (0 to 0)***	3 (2-6)
Duration of mechanical ventilation in days, median [IQR]	2 (0-6)	2 (0-5)	*0.0 (0 to 0)***	2 (0-7)
Length of stay ICU, median [IQR]	4 (2-9)	4 (2-8)	*0.0 (0 to 0)***	4 (2-9)
Length of stay hospital, median [IQR]	15 (9-27)	14 (9-25)	*0.0 (0 to 0)***	16 (9-30)
Incidence of ICU re-admission, n (%)	62 (9.1)	67 (10.1)	*1.0 (-4.2-2.3)*	34 (10.3)
Incidence of physical restraints, n (%)	173 (26.2)	158 (24.5)	*1.7 (-3.2-6.6)*	93 (28.8)
Incidence of unplanned removal of tubes, catheters, n (%)	77 (11.3)	69 (10.3)	*1.0 (-2.5-4.4)*	40 (12.1)
Incidence of re-intubation, n (%)	65 (9.5)	59 (8.9)	*0.7 (-2.5-3.9)*	27 (8.2)
Safety issues				
Maximum QTc-time in msec., median [IQR]	465 (446-484)	462 (440-	*1.0 (-1.0-5.0)***	462 (440-485)
- number of QTc-time prolongations, n (%)	29 (4.3)	485)	*-1.0 (-3.4-1.4)*	28 (8.5)
Incidence of extra-pyramidal symptoms		35 (5.2)		
- dystonia	1 (0.1)		*0.2 (-0.8-5.0)*	3 (0.9)
- tremor	6 (0.9)	3 (0.4)	*-0.1 (-1.0-1.2)*	6 (1.8)
- myoclonus	4 (0.6)	6 (0.9)	*-0.1 (-0.8-0.8)*	4 (1.2)
- tics	4 (0.6)	5 (0.7)	*-0.3 (-1.4-0.8)*	4 (1.2)
- rigidity	3 (0.4)	6 (0.9)	*-0.3 (-1.3-0.7)*	3 (0.9)
- akathasia	4 (0.6)	5 (0.7)	*-0.1 (-0.8-1.0)*	6 (1.8)
		3 (0.4)		
Reported Serious Adverse Events, n (%)	0 (0)	1 (0.1)	*-0.1 (-0.6-0.3)*	1 (0.3)

** Differences between medians are described as absolute difference in ranking following order


Hazard Ratio
6
5
4
3
2
1
0
1mg haloperidol
2mg haloperidol
Monitoring boundary for benefit
Area of benefit
Futility area
Area of harm
Monitoring boundary for harm
0
100
200
300
Number of events


Subgroup
Haza rd ratio – 28 d ays su rvival
HR
95%CI
P-value for interaction
Diagnose g roup
Surgical 0.95 [0.62; 1.45] 0.78
Medical 0.98 [0.71; 1.34]
Trauma 2.18 [0.23; 20.97]
APACHE–II
APACHE–II <20 0.84 [0.54; 1.32] 0.71
APACHE–II 20–30 0.92 [0.57; 1.49]
APACHE–II >30 1.08 [0.73; 1.59]
PRE–DELIRIC score
PRE–DELIRIC <20 0.62 [0.30; 1.31] 0.35
PRE–DELIRIC 20–30 1.19 [0.72; 1.97]
PRE–DELIRIC >30 0.91 [0.66; 1.25]
Duration of pr eventive treatment – 2 d ays
2 d ays 0.82 [0.57; 1.16] 0.17
> 2 d ays 1.16 [0.81; 1.67]
Duration of pr eventive treatment – 3 d ays
3 d ays 0.82 [0.59; 1.14] 0.12
> 3 d ays 1.24 [0.83; 1.83]
Duration of pr eventive treatment – 5 d ays
5 d ays 0.90 [0.67; 1.20] 0.34
> 5 d ays 1.19 [0.72; 1.96]
Delirium
Non–deli rium patients 1.02 [0.75; 1.39] 0.58
Deli rium patients 0.88 [0.57; 1.34]
0.3
0.5
1
2
3
Halope ridol 2mg better
Placebo better


Subgroup
Haza rd ratio – 90 d ays su rvival
HR
95%CI
P-value for interaction
Di agnose g roup
Surgical
1.00 [0.69; 1.45] 0.78
Medical
0.96 [0.72; 1.28]
Trauma
2.18 [0.23; 20.97]
A PA CHE–II
A PACHE–II <20
0.87 [0.59; 1.29] 0.70
A PACHE–II 20–30
0.92 [0.60; 1.43]
A PACHE–II >30
1.08 [0.76; 1.54]
PRE–DELIRIC score
PRE–DELIRIC <20
0.60 [0.31; 1.15] 0.32
PRE–DELIRIC 20–30
1.08 [0.71; 1.66]
PRE–DELIRIC >30
0.97 [0.72; 1.29]
Duration of pr eventive treatment – 2 d ays
2 d ays
0.86 [0.63; 1.17] 0.21
> 2 d ays
1.14 [0.82; 1.58]
Duration of pr eventive treatment – 3 d ays
3 d ays
0.83 [0.62; 1.11] 0.08
> 3 d ays
1.26 [0.88; 1.80]
Duration of pr eventive treatment – 5 d ays
5 d ays
0.94 [0.72; 1.22] 0.56
> 5 d ays
1.09 [0.70; 1.72]
Delirium
Non–deli rium patients
1.00 [0.75; 1.32] 0.81
Deli rium patients
0.94 [0.64; 1.37]
0.3
0.5
1
2
3
Halope ridol 2mg better
Placebo better


Study
Odds ratio – Delirium incidence
OR
95%CI
P-value for interaction
Diagnose group
Surgical 1.19 [0.87; 1.62] 0.35
Medical 0.89 [0.64; 1.24]
Trauma 0.64 [0.19; 2.11]
APACHE–II
APACHE–II <20 1.09 [0.80; 1.47] 0.43
APACHE–II 20–30 1.11 [0.71; 1.76]
APACHE–II >30 0.77 [0.49; 1.22]
PRE–DELIRIC score
PRE–DELIRIC <20 1.00 [0.63; 1.57] 0.58
PRE–DELIRIC 20–30 1.13 [0.77; 1.66]
PRE–DELIRIC >30 0.86 [0.60; 1.22]
Duration of preventive treatment – 2 days
2 days 0.90 [0.66; 1.21] 0.23
> 2 days 1.17 [0.85; 1.62]
Duration of preventive treatment – 3 days
3 days 1.03 [0.78; 1.36] 0.84
> 3 days 0.98 [0.68; 1.42]
Duration of preventive treatment – 5 days
5 days 1.02 [0.79; 1.30] 0.92
> 5 days 0.99 [0.61; 1.61]
0.3
0.5
1
2
3
Haloperidol 2mg better
Placebo better