Baseline characteristics and treatment-emergent risk factors associated with cerebrovascular event and death with risperidone in dementia patients

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Structured abstract

Background: Use of antipsychotics to treat behavioural symptoms of dementia has been associated with increased risks of mortality and stroke. Little is known about individual patient characteristics that might be associated with bad or good outcomes.

Aims: We examined the risperidone clinical trial data to look for individual patient characteristics associated with these adverse outcomes.

Method: Data from all double-blind, RCTs of risperidone in dementia patients (1009 risperidone, 712 placebo) were included. Associations between characteristics and outcome were analysed based on crude incidences, exposure-adjusted incidence rates, and by time-to-event analyses using Cox proportional hazards regression. Interactions between treatment (risperidone or placebo) and characteristic were analysed with a Cox proportional hazards regression model with main effects for treatment and characteristic in addition to the interaction term.

Results: Baseline complications of depression (treatment by risk factor interaction on CVAE hazard ratio [HR]: $p = 0.025$) and delusions ($p = 0.043$) were associated with a lower relative risk of CVAE in risperidone treated patients (HR=1.47 and 0.54, respectively) compared to not having the complication (HR=5.88 and 4.16). For mortality, the only significant baseline predictor in patients treated with risperidone was depression, which was associated with a lower relative risk ($p<0.001$). The relative risk of mortality was increased in risperidone patients treated with anti-inflammatory medications ($p=0.021$).

Conclusions: Only anti-inflammatory medications increased mortality risk with risperidone. The reduced risk of CVAE in patients with co-morbid depression and delusions, and of mortality with depression may have clinical implications when weighing the benefits and risks of treatment with risperidone in patients with dementia.

Declaration of interest: KK, DC and DH are employees of Janssen Research and Development and are owners of Johnson and Johnson stock. JB is an employee of Johnson and Johnson and is an owner of Johnson and Johnson stock. RH has received medication from Pfizer-Eisai and Lundbeck for an independent clinical trial on which he was Chief Investigator. SGC reports no financial relationships with commercial interests.

Introduction

Risperidone is licenced by the European Medicines Agency for the short-term (up to 6 weeks) treatment of persistent aggression in patients with moderate to severe Alzheimer's dementia unresponsive to non-pharmacological approaches and when there is a risk of harm to self or others (1). Meta-analysis of primary efficacy and safety data from four of the risperidone trials has been published (2), together with an analysis of mortality in six studies (3). As physicians who are frequently faced by decisions about treatment in this situation, RH and SGC approached Janssen with two questions. First, given the known risks of risperidone treatment in this population (3-7), were there baseline characteristics of individual patients within the clinical trials database that could be used to identify those at higher (or lower) risk of death or CVAE associated with risperidone treatment? Second, once treatment had been initiated, which treatment-emergent events were associated with risk of subsequent death or CVAE in patients treated with risperidone? We conducted a meta-analysis of all Janssen's double-blind randomized controlled trials of risperidone in dementia to address these questions, with a focus on identifying patient characteristics and treatment emergent events that would result in differential risk of stroke and death to risperidone and placebo.

Methods

Study Selection

Data from all 6 randomized, double-blind, placebo-controlled studies of risperidone in elderly patients with dementia conducted by Janssen were included in this analysis. The primary results of four of the studies (USA-63 (NCT00253123) (8), INT-24 (NCT00249145) (9), AUS-5 (NCT00249158) (10), and USA-232 (NCT00034762) (11)) have been previously published. The current analysis also includes 2 studies which were not published due to insufficient numbers of subjects: a pilot study, BEL-14 (N=39), and INT-83 (N=18), which was terminated for (non-clinical) business reasons.

Detailed study design characteristics are available in the primary publications. All included males and females aged ≥55 years with Alzheimer's, vascular, or mixed dementia as classified by the Diagnostic and Statistical Manual of Mental Diseases, 4th Edition (DSM-IV) (12). In 4 studies (USA-63, INT-24, AUS-5, BEL-14), a BEHAVE-AD (13) total score ≥8 and a BEHAVE-AD global rating of ≥1 were inclusion criteria. In USA-232 and INT-83, a score of ≥2 on any item of the BEHAVE-AD psychosis subscale was an inclusion criterion. Treatment duration was 12 weeks for USA-63, INT-24, and AUS-5; 8 weeks for USA-232 and INT-83; and 4 weeks for BEL-14. USA-63 included 3 fixed dose arms of risperidone (0.5, 1, or 2 mg daily). Flexible dosing was employed in the other studies, with total daily dose ranges of 0.5-4 mg in INT-24, 0.5-2 mg in AUS-5, 1-4 mg in BEL-14, and 1-1.5 mg in USA-232 and INT-83. For the current analysis, all risperidone doses were combined into a single group.

Variable Definitions

The following baseline characteristics were examined for an association with CVAE or mortality: age (<80 years vs. ≥80 years), sex, race, diagnosis, body mass index (BMI), Mini-Mental State Examination (14), BEHAVE-AD delusion-related items, BEHAVE-AD global rating, creatinine clearance , diastolic blood pressure, pulse, blood levels of sodium and urea, cardiovascular, neurological, or respiratory findings on medical history, and cardiovascular, neurological, or respiratory findings on baseline physical examination. Detailed criteria for each baseline characteristic are in the full statistical analysis plan available on-line.

Treatment-emergent events examined for an association with CVAE or mortality included weight increase (≥7% increase), weight decrease (≥7% decrease), creatinine clearance decrease (≥10% and ≥20%), diastolic blood pressure (>90 mmHg), sedation, malnutrition, dehydration, extrapyramidal symptoms, pulmonary condition, infection (urinary or pulmonary), and cardiovascular disease adverse events. A treatment-emergent event was considered 'present' only if the earliest occurrence of the event preceded the CVAE or death. In an additional analysis, the treatment-emergent event was considered 'present' only if the earliest occurrence of the event preceded the CVAE or death by at least 7 days.

Selected categories of concomitant medications, based on the WHO Drug Dictionary Anatomic-Therapeutic-Chemical (ATC) class, were also examined for their association with CVAE or mortality: potentially sedating medications, anti-inflammatory drugs, beta blockers, diuretics, and laxatives. Concomitant medication use was defined in the same ways as the presence of a treatment-emergent event, based on the earliest start date of the concomitant medication (medications with a missing start date were considered to have been present from baseline).

Statistical Methods

For analysis of differences between risperidone and placebo in individual studies, Fisher's exact test was used to compare the crude incidences of CVAE and mortality and Wald's method was used to compare exposure adjusted incidence rates (EAIRs) (15). Analysis based on the combined studies used the Cochran-Mantel-Haenszel test for crude incidence and the Mantel-Haenszel-type method of Greenland and Robins (16) for EAIRs.

The association between a CVAE or mortality and a baseline characteristic or treatment-emergent event (including concomitant medication use) was analysed by Fisher's exact test for crude incidence and Wald's method for EAIR. The placebo group only were included in these analyses and the analysis was based on the cross-tabulation of the event of interest (CVAE or mortality) versus the characteristic (baseline or treatment-emergent). For treatment-emergent events, an additional analysis by Cox proportional hazards regression was performed with the treatment-emergent event as a time-varying covariate. Analyses of treatment-emergent events were performed for both definitions of being present (earliest onset before the CVAE or mortality and earliest onset ≥7 days before the CVAE or mortality). In the Cox regression, the treatment-emergent event was considered present from the time of its onset, however defined, until the onset of the CVAE or mortality or until study discontinuation for subjects who did not have a CVAE or die. In this way, the treatment-emergent event is considered to become a subject characteristic at the time of its onset.

To evaluate how a baseline characteristic or treatment-emergent event modified the difference between risperidone and placebo, a Cox regression with factors of treatment group, baseline characteristic or treatment-emergent event, and the interaction of treatment and baseline characteristic or treatment-emergent event was performed. Treatment-emergent events (including concomitant medications) were included as time-varying covariates as described above. The significance of the interaction term was based on likelihood ratio statistics comparing the models with and without that term. Hazard ratios (HRs) and 95% confidence intervals comparing risperidone and placebo were estimated from the full model at both levels of the baseline characteristic or treatment-emergent event.

All statistical analyses were performed using SAS Version 9.2 (17). Figures were generated using the R `lattice` package (18).

Nominal p-values are presented throughout; there was no adjustment for multiplicity.

Results

(1) Overall and comparative incidence of CVAE and mortality in all patients with dementia and behavioural symptoms treated with risperidone or placebo

1009 risperidone- and 712 placebo-treated patients were included in the combined database. Demographic features of patients are reported in Table 1.

There was a statistically significant difference in the crude incidence of all CVAEs across all studies: risperidone (49/1009, 4.9%) and placebo (11/712, 1.5%); ($p<0.001$, Cochran-Mantel-Haenszel test stratified by study) (Table 2). Crude incidence of mortality was numerically higher in the risperidone (40/1009, 4.0%) than placebo (22/712, 3.1%) group, but the between-group difference was not statistically significant ($p=0.527$, Cochran-Mantel-Haenszel test stratified by study). The risperidone group had a statistically significantly higher exposure-adjusted incidence of any CVAE across all studies compared to placebo ($p<0.001$). Exposure-adjusted incidence of mortality was higher in the risperidone group compared to the placebo group, but this was not statistically significant ($p=0.466$).

(2) *Risk Factors in patients with dementia and behavioural symptoms treated with placebo*

Baseline patient characteristics that predicted CVAE or Mortality in patients treated with placebo: crude incidence analysis

Figure 1 summarizes the crude incidence of CVAEs and mortality in placebo patients with and without the identified risk factors. Placebo patients with age>80 years ($p=0.020$) and with baseline depressed mood ($p=0.047$) were at increased risk of CVAE. Analysis of potential baseline risk factors for mortality indicated that severe impairment of creatinine clearance ($p=0.024$) and depressed mood ($p=0.023$) were significantly associated with increased mortality, while male sex ($p=0.056$) and severe dementia (MMSE<9) ($p=0.087$) failed to reach accepted significance levels.

Baseline patient characteristics that predicted CVAE or Mortality in patients treated with placebo: exposure-adjusted incidence rate (EAIR)

Analyses based on EAIR differences between placebo patient characteristic groups identified age>80 years ($p=0.004$) and BEHAVE global rating less than severe ($p=0.045$) as significant risk factors for CVAE, while cardiovascular medical history ($p=0.073$) failed to reach accepted significance levels. No significant risk factors for mortality were identified, with age>80 ($p=0.096$), severe impairment of creatinine clearance ($p=0.093$), depressed mood ($p=0.074$) and male sex ($p=0.081$) failing to reach significance.

Treatment-emergent adverse event risk factors (TERF) that predicted CVAE or Mortality in patients treated with placebo: crude incidence analysis

No TERFs were significantly associated with CVAE. TERFs associated with increased mortality included dehydration ($p<0.001$), infection ($p<0.001$) and pulmonary conditions ($p=0.012$), while cardiovascular disease ($p=0.058$) and sedation ($p=0.068$) failed to reach accepted significance levels. (See Figure 2).

Treatment-emergent adverse event risk factors (TERF) that predicted CVAE or Mortality in patients treated with placebo: exposure-adjusted incidence rate

For EAIR of CVAE by TERF none of the examined risk factors was significantly associated. For EAIR of mortality by TERF, dehydration (p=0.042) and infection (p=0.007) emerged as significant, while pulmonary conditions (p=0.056) failed to reach significance.

Cox regression did not identify TERFs significantly associated with CVAE. Risk factors for mortality confirmed as statistically significant by Cox regression included cardiovascular TEAE (HR=9.68; 95% CI: 2.2 to 42.65; p=0.022), creatinine clearance decrease >20% (HR=9.86; 95% CI: 1.98 to 49.07; p=0.024), dehydration (HR=31.61; 95% CI: 10.49 to 95.25; p<0.001), infection (HR=5.82; 95% CI: 2.39 to 14.18; p<0.001) and pulmonary condition (HR=5.22; 95% CI: 2.07 to 13.12; p=0.001). Weight decrease >7% (HR=5.87; 95% CI: 1.22 to 28.26; p=0.065) and sedation (HR=3.05; 95% CI: 1.09 to 8.52; p=0.054) failed to reach significance levels.

Treatment-emergent adverse events risk factors (TERF) that predicted CVAE or Mortality in patients treated with placebo: TERF analysis with 7-day offset

For the crude incidence of CVAE, no TERF was statistically significant. For the crude incidence of mortality, significant TERFs identified included dehydration (p=0.013), infection (p=0.004), and pulmonary condition (p=0.050), while weight decrease >7% (p=0.081) did not reach statistical significance.

Analyses based on exposure-adjusted incidence rate differences between TEAE groups (results available online) did not identify any new risk factors for CVAE compared to analysis of crude incidence and only infection (p=0.045) was significantly associated with mortality. Analyses based on the Cox regression identified the same risk factors for increased mortality as analysis without the 7-day offset, together with an additional risk factor, weight decrease >7% (HR=6.68; 95% CI: 1.4 to 31.88; p=0.050).

Effects of concomitant medication use on risk of CVAE or mortality in placebo patients

There was a non-significant trend for anti-inflammatory drugs to be associated with a lower risk of death in the EAIR analyses (p=0.081) and for sedating medications to be associated with increased mortality based on Cox regression (HR=2.15; 95% CI: 0.86 to 5.4; p=0.094).

(3) Risk Factors in patients with dementia and behavioural symptoms treated with risperidone

This analysis investigated which factors conferred a difference in risk between patients treated with risperidone relative to those treated with placebo, as evidenced by a significant treatment-by-risk factor interaction in the Cox regression between the HR of risperidone and placebo in those with or without the risk factor. Results for those baseline characteristics, TERFs, or concomitant medications that had a statistically significant treatment-by-factor interaction term are summarized in Table 3A for CVAE and Table 3B for mortality.

Baseline patient characteristics that modified the differential risk for CVAE and mortality in patients treated with risperidone compared to placebo

For CVAE, a significant interaction effect was observed for age>=80 years, positive cardiovascular medical history, baseline delusions, and baseline depressed mood. For baseline delusions and depressed mood, the risperidone:placebo HR was lower in patients with the complication (1.47, 95% CI: 0.59 to 3.65 for delusions; 0.54, 95% CI: 0.12 to 2.40 for depressed mood) compared to patients

without the complication (5.88, 95% CI: 2.09 to 16.53 for delusions; 4.16, 95% CI: 1.96 to 8.82 for depressed mood). For age>=80 years and cardiovascular medical history, the significant interaction was likely the result of no placebo patients without the baseline characteristic having a CVAE. The relative risk of CVAE among subjects with age>=80 years or with cardiovascular medical history is similar to the relative risk among all patients as shown in Table 2.

For mortality, a significant interaction effect was observed for baseline depressed mood with more deaths in the placebo group (5/54, 9.3%) than in the risperidone group (0/112) among patients with baseline depressed mood compared to more deaths in the risperidone group compared to the placebo group among patients without depressed mood at baseline (HR=1.52, 95%: 0.86 to 2.70).

Treatment emergent risk factors that modified the differential risk for CVAE and mortality in patients treated with risperidone compared to placebo

Only creatinine clearance decrease of >20% was associated with a modified hazard ratio for mortality (HR if risk factor present undefined as no CVAEs in risperidone group; HR if risk factor not present=2.49; 95% CI 1.24 to 5.02; p=0.049). There was only 1 event (in a placebo-treated subject vs. no events in the risperidone-treated group) among those with the creatinine clearance decrease. There were no TERFs associated with an excess mortality risk in patients treated with risperidone when compared with placebo-treated patients.

Concomitant medication use that modified the differential risk for CVAE and mortality in patients treated with risperidone compared to placebo

There were no concomitant medications whose use was associated with differential CVAE risk in patients treated with risperidone compared to placebo. The treatment-by-risk factor interaction term was statistically significant for analyses of mortality for anti-inflammatory drug use, with a higher risperidone:placebo hazard ratio in patients with use of these drugs (HR if risk factor present=3.42; 95% CI: 1.00 to 11.76; HR if risk factor not present=0.78; 95% CI: 0.42 to 1.43; p=0.021). The presence or absence of the 7-day offset did not change this result.

Discussion

Meta-analyses of clinical trials in elderly patients with dementia indicate that individual antipsychotic drugs have different mortality risks, with quetiapine being associated with the lowest, and haloperidol being associated with the highest risk of death (6,7,19,20). For a given drug, there is a dose-response relationship with mortality (7). A physician, faced with a patient whose symptoms and behaviour are distressing and can place the patient and others at significant danger, needs to evaluate the potential benefits on balance with the risks of treatment in an individual case (21). For example, depending on the atypical antipsychotic, the number of patients that would need to be treated to observe improvement in psychosis and aggression in a single patient ranges from 5 to 14 (5), with quetiapine having less convincing evidence for efficacy than risperidone and olanzapine (7,22). There is a significant chance that psychosis symptoms will return when treatment is stopped (23). The most extreme contrasting risk of treatment is reflected by the number of patients needed to be treated to observe a single death, ranging from 27 to 100 (4,7).

In terms of baseline patient factors associated with increased exposure-adjusted incidence of CVAE in placebo-treated patients, we confirmed the previously reported age>80, as well as finding the novel BEHAVE global rating less than severe, while no significant risk factors for mortality were identified by this method. No treatment-emergent events were associated with increased exposure-adjusted incidence of CVAE in placebo-treated patients. Treatment-emergent events associated with increased exposure-adjusted incidence of mortality were dehydration, infection, and pulmonary conditions. Baseline characteristics that modified the risk of CVAE in patients treated with risperidone compared to placebo included age>=80 and cardiovascular disease history. Presence of delusions or depressed mood at baseline was associated with a lower risperidone:placebo hazard ratio for CVAE compared to not having those complications. Baseline depressed mood was also associated with a reduced risperidone:placebo hazard ratio for mortality. None of the investigated treatment emergent risk factors modified the differential risk for CVAE and mortality in patients treated with risperidone compared to placebo except for creatinine clearance decrease >20%, which was associated with a reduced hazard ratio for CVAE. This is hard to explain and may be a consequence of the very small number of patients with an observed creatinine clearance decrease prior to a CVAE. There was only one CVAE in a placebo-treated patient versus none in the risperidone group among participants with the creatinine clearance decrease. We also found that concomitant use of anti-inflammatory drugs was associated with a greater risperidone:placebo hazard ratio for mortality compared to no use of such drugs.

Our data show some overlap with the results of the analysis of the integrated olanzapine database (24), which identified age>80, concomitant benzodiazepine use, treatment-emergent sedation and pulmonary conditions to be associated with an increased risk of mortality, and that age>80 and diagnosis of vascular or mixed dementia were associated with an increased risk of CVAE. However, this analysis identified risk factors in a combined sample of patients treated with olanzapine or placebo. Their results would therefore reflect a combination of background risk factors for CVAE and death in a general elderly population (from placebo patients), with specific risk factors for an adverse outcome in patients treated with olanzapine. By examining for characteristics that modified risk in patients treated with risperidone compared to placebo, rather than simply in the combined trial population, we were able to identify patient related factors that could potentially inform a more individualised benefit-risk analysis in the initiation of antipsychotic treatment.

The association of delusions or depression with reduced CVAE risk and depression with reduced mortality in risperidone compared with placebo-treated patients may indicate that specific psychiatric symptoms, rather than clusters of behaviours such as agitation, marks patients for whom atypical antipsychotic treatment carries less risk. In the Clinical Antipsychotic Trials of Intervention Effectiveness-Alzheimer's Disease (CATIE-AD) study (25), specific symptoms including paranoid ideas were more likely to improve with atypical antipsychotic treatment (26). Also, in a meta-analysis of placebo-controlled risperidone trials (2), "people are stealing things" or infidelity delusions were more likely to respond to treatment than other symptoms. A meta-analysis of atypical trials in dementia, however, reported smaller treatment effect sizes for patients selected on the basis of psychosis symptoms (27), so the literature is not consistent. Our data add to evidence that delusions may represent a target symptom in AD where potential treatment benefits are significant and risks of CVAE smaller. This finding will need to be replicated in an independent sample before it can form the basis for advice to guide clinicians when making decisions about stratifying risk in this treatment indication. However, our data add to an emerging story that the presence of particular individual psychiatric symptoms in patients with dementia is associated with both the potential benefits and risks of antipsychotic treatment.

Although anti-inflammatory drugs are associated with increased cardiovascular events and all-cause mortality in the general medical population (28), these agents did not increase the risk of stroke or death in placebo patients in the trials examined here. The increased relative mortality in risperidone patients who also were treated with anti-inflammatory medications represents an easily modifiable risk factor in clinical practice.

A limitation of our findings is that, as in previous investigations of potential risk factors for stroke and death in dementia patients treated with an atypical antipsychotic by other authors (24), we did not make statistical correction of our results for the effects of multiple comparisons. We would acknowledge that some of our findings, with p values in the 0.02 to 0.05 range, might have arisen by the effects of chance and the multiple statistical comparisons made in our analyses. We would argue that this is unlikely, and that the consistency of the findings with what we understand clinically and with each other argues against such a negative explanation.

Clinicians will continue to consider antipsychotic short term treatment for behavioural and psychiatric symptoms in dementia when those symptoms cause significant distress or carry risk of harm to the patient or others, and when alternative, non-pharmacological interventions are unavailable or have failed (21,39). These symptoms are independently associated with more rapid progression to severe dementia and earlier death (30) and their treatment represents a potential opportunity to modify the clinical course of dementia. Our analysis has confirmed some of the previously established patient factors associated with increased risk of CVAE and mortality during antipsychotic treatment. Importantly, we have also reported that the presence of some psychiatric symptoms was associated with reduced risk of CVAE and mortality within the population of dementia patients treated with risperidone in the pivotal trials.

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Table 1: Demographics of patients in double-blind placebo-controlled risperidone studies

Characteristic Parameter	PLACEBO (N=712)	RISPERIDONE (N=1009)	HALOPERIDOL (N=115)	Total (N=1836)
Age, years				
N	712	1009	115	1836
Mean (SD)	82.2 (7.69)	82.7 (7.24)	81.0 (7.60)	82.4 (7.45)
Median	83.0	83.0	82.0	83.0
Range	56 - 100	58 – 105	56 – 97	56 - 105
Sex, n (%)				
N	712	1009	115	1836
Female	498 (70)	702 (70)	62 (54)	1262 (69)
Male	214 (30)	307 (30)	53 (46)	574 (31)
Race, n (%)				
N	693	989	115	1797
Black	36 (5)	65 (7)	0	101 (6)
Caucasian	623 (90)	885 (89)	115 (100)	1623 (90)
Hispanic	20 (3)	22 (2)	0	42 (2)
Oriental	11 (2)	11 (1)	0	22 (1)
Other	3 (<1)	5 (1)	0	8 (<1)
Polynesian	0	1 (<1)	0	1 (<1)
Weight, kg				
N	689	980	108	1777
Mean (SD)	60.29 (13.084)	59.74 (13.117)	62.26 (12.334)	60.11 (13.065)
Median	59.02	58.11	60.00	59.00
Range	33.2 - 112.7	30.0 - 145.4	40.0 - 90.0	30.0 - 145.4
Height, cm				
N	675	956	96	1727
Mean (SD)	160.84 (10.912)	160.54 (10.794)	162.91 (10.183)	160.79 (10.814)
Median	160.02	160.02	163.00	160.02
Range	115.0 - 196.0	115.0 – 198.1	144.0 - 192.0	115.0 - 198.1
Body Mass Index, kg/m^2				
N	667	943	96	1706
Mean (SD)	23.32 (4.650)	23.22 (4.548)	23.57 (4.205)	23.28 (4.568)
Median	22.80	22.80	23.35	22.80
Range	13.3 - 51.9	11.3 - 54.7	16.1 - 35.8	11.3 - 54.7
Baseline MMSE total score				
N	699	988	114	1801
Mean (SD)	9.0 (6.63)	8.3 (6.63)	8.0 (6.52)	8.5 (6.63)
Median	9.0	8.0	8.0	8.0
Range	0 - 23	0 – 24	0 – 22	0 - 24
Baseline FAST highest score				
N	447	741	115	1303
Mean (SD)	10.2 (2.68)	10.4 (2.57)	9.8 (2.68)	10.2 (2.62)
Median	10.0	10.0	10.0	10.0
Range	4 - 16	4 – 16	4 – 16	4 - 16

Table 2: Crude incidence of mortality and CVAE in risperidone studies

	Mortality			Any CVAE		
Study	n/N	%	P-value[a]	n/N	%	P-value[a]
All studies						
Risperidone	40/1009	4.0	0.527	49/1009	4.9	<0.001
Placebo	22/712	3.1		11/712	1.5	
AUS-5						
Risperidone	6/167	3.6	0.769	18/167	10.8	0.002
Placebo	5/170	2.9		4/170	2.4	
BEL-14						
Risperidone	1/20	5.0	1.000	0/20	0	--
Placebo	0/19	0		0/19	0	
INT-24						
Risperidone	1/115	0.9	0.119	12/115	10.4	0.010
Placebo	5/114	4.4		2/114	1.8	
INT-83						
Risperidone	0/10	0	0.444	1/10	10.0	1.000
Placebo	1/8	12.5		0/8	0	
USA-232						
Risperidone	9/235	3.8	0.445	5/235	2.1	0.283
Placebo	6/238	2.5		2/238	0.8	
USA-63						
Risperidone	23/462	5.0	0.383	13/462	2.8	0.773
Placebo	5/163	3.1		3/163	1.8	

[a] Cochran-Mantel-Haenszel test stratified by study for 'All Studies'; Fisher's exact test for individual studies.

Table 3A: Treatment-by-Factor Incidence of Any CVAE – Factors with Treatment-by-Factor Interaction P-value <0.05 (Cox Regression)

	Present			Not Present			
	Risperidone	Placebo	RIS:PLA HR (95% CI)	Risperidone	Placebo	RIS:PLA HR (95% CI)	Interaction p-value[a]
Age ≥80 years	40/697 (5.7%)	11/466 (2.4%)	2.41 (1.24, 4.70)	9/312 (2.9%)	0/246	--	0.032
Cardiovascular Medical History	27/677 (4.0%)	9/472 (1.9%)	2.01 (0.95, 4.28)	10/196 (5.1%)	0/107	--	0.036
Delusions (diagnosis)	14/459 (3.1%)	7/347 (2.0%)	1.47 (0.59, 3.65)	35/530 (6.6%)	4/346 (1.2%)	5.88 (2.09, 16.53)	0.043
Depressed Mood (diagnosis)	4/112 (3.6%)	3/54 (5.6%)	0.54 (0.12, 2.40)	45/877 (5.1%)	8/639 (1.3%)	4.16 (1.96, 8.82)	0.025
Creatinine Clearance decrease ≥20% (treatment-emergent)	0/63	1/39 (2.6%)	--	36/794 (4.5%)	10/559 (1.8%)	2.49 (1.24, 5.02)	0.049
Creatinine Clearance decrease ≥20% (treatment-emergent with 7-day rule)	0/41	1/23 (4.4%)	--	36/816 (4.4%)	10/575 (1.7%)	2.49 (1.24, 5.02)	0.049
Beta Blockers (treatment-emergent)	9/124 (7.3%)	0/89	--	40/885 (4.5%)	11/623 (1.8%)	2.54 (1.30, 4.95)	0.041

[a] Likelihood ratio test of treatment-by-factor interaction term in Cox proportional hazards regression.

Table 3B: Treatment-by-Factor Incidence of Death – Factors with Treatment-by-Factor Interaction P-value <0.05 (Cox Regression)

	Present			Not Present			
	Risperidone	Placebo	RIS:PLA HR (95% CI)	Risperidone	Placebo	RIS:PLA HR (95% CI)	Interaction p-value
Depressed Mood (diagnosis)	0/112	5/54 (9.3%)	--	39/877 (4.4%)	17/639 (2.6%)	1.52 (0.86, 2.70)	<0.001
Anti-inflammatory medications (treatment-emergent)	16/310 (5.2%)	3/213 (1.4%)	3.42 (1.00, 11.76)	24/699 (3.4%)	19/499 (3.8%)	0.78 (0.42, 1.43)	0.021
Anti-inflammatory medications (treatment-emergent with 7-day rule)	16/310 (5.2%)	3/211 (1.4%)	3.42 (1.00, 11.75)	24/699 (3.4%)	19/501 (3.8%)	0.78 (0.42, 1.43)	0.021

[a] Likelihood ratio test of treatment-by-factor interaction term in Cox proportional hazards regression.

Figure 1: Incidence of Cerebrovascular Adverse Event and Mortality by Baseline Risk Factor – Placebo Subjects

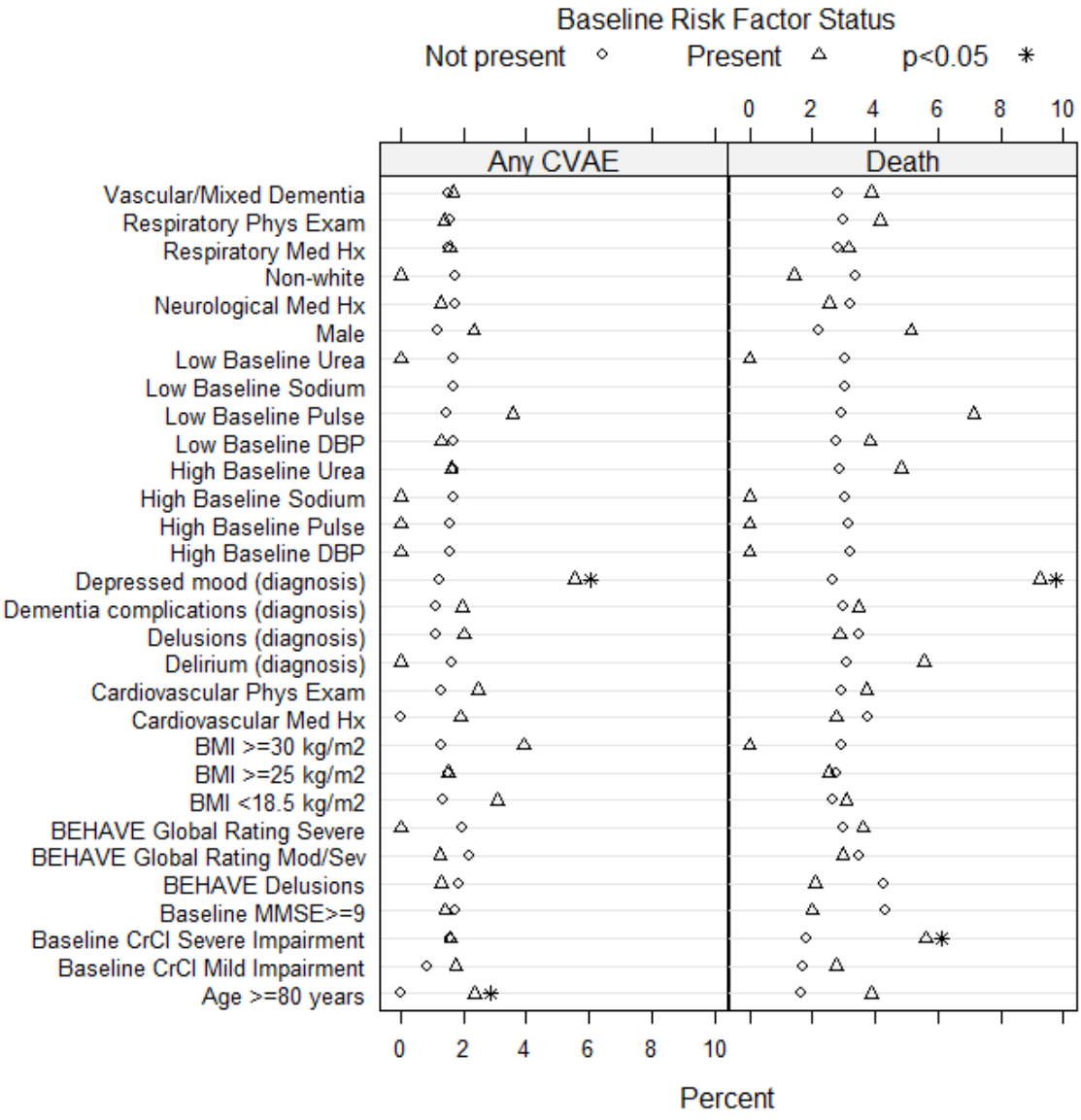

Figure 2: Incidence of CVAE and Mortality by Treatment-emergent Risk Factor – Placebo Subjects