Title:

Tolerability and safety profile of cariprazine in treating psychotic disorders, bipolar disorder and major depressive disorder: a systematic review with meta-analysis of randomized controlled trials

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Short title:

Tolerability/safety of cariprazine

Compliance with ethical standards:

This work was not supported by any funding. Regarding authors' contribution, KSJL, ICKW and EWC had the original idea for this study and contributed to the development of the idea and study design. KSJL and YH independently conducted a systematic review and reviewed the literature for relevance. KSJL and YH undertook the analysis. KSJL, YH, ICKW and EWC contributed to interpretation of the analysis. KSJL and YH wrote the first draft of the paper. KSJL, YH, ICKW and EWC critically reviewed the results and the manuscript. FMCB

reviewed the data and presentation of the paper, and provided clinical input. ICKW and EWC provided oversight to all aspects of this project. KSJL and EWC are the guarantors. All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of data analysis.

Conflicts of interest:

Authors KSJL, YH, ICKW, FMCB and EWC declare no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted study.

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Supplementary Table 1. Assessment of the risk of bias in accordance with the Cochrane Collaboration tool*

Study	Sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective outcome reporting	Other sources of bias
Calabrese 2015 [20]	Unclear	Unclear	Unclear	Yes	Yes	Yes
Durgam 2014 [16]	Unclear	Unclear	Unclear	Unclear	Yes	Yes
Durgam 2015a [19]	Unclear	Unclear	Unclear	Yes	Yes	Yes
Durgam 2015b [21]	Yes	Yes	Yes	Yes	Yes	Yes
Durgam 2015c [15]	Unclear	Unclear	Unclear	Yes	Yes	Yes
Durgam 2015d [17]	Unclear	Unclear	Unclear	Yes	Yes	Yes
Kane 2015 [14]	Unclear	Unclear	Unclear	Yes	Yes	Yes
Sachs 2015 [18]	Unclear	Unclear	Unclear	Yes	Yes	Yes
Durgam 2016 [22]	Yes	Yes	Yes	Yes	Yes	Yes

*Yes: low risk of bias. These domains were considered to be less vulnerable to bias for following reasons: detailed methods of randomization were reported clearly; there was no missing data or missing outcome data was balanced across intervention groups or had been imputed using statistical methods; the outcomes were pre-specified and reported or; the study appeared to be free of other sources of bias. For example, Durgam 2015b [21] used computer-generated randomization list for sequence generation, and the study drug was identical in appearance. Durgam 2016 [22] reported that an interactive voice/web system was applied to generate a randomization list and study drug was identical in appearance. Therefore, risk of bias in respective domains were rated as "low risk of bias."

Unclear: domains were marked "unclear risk of bias" due to insufficient information reported. For example, subjects in these studies were randomly assigned, however the details of methods applied in sequence generation, allocation concealment and blinding were not reported. In Durgam 2014, the number of subjects who discontinued treatment in cariprazine and placebo groups were different, which might affect the estimation of safety outcomes as they were analyzed based on safety population, however the effect was not

clear. The details of the quality assessment criteria were based on the Cochrane handbook [45].

Supplementary Table 2. Evidence profile table

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	cariprazine	placebo	Relative (95% CI)	Absolute (95% CI)		
Discontinuation due to AEs (follow up: range 3 weeks to 8 weeks)												
9	randomised trials	not serious	serious [1]	not serious	serious [2]	none	285/2900 (9.8%)	125/1424 (8.8%)	**RR 1.13** (0.77 to 1.66)	**11 more per 1,000** (from 20 fewer to 58 more)	⊕⊕◯◯ LOW	CRITICAL
Potentially clinically significant change in weight (follow up: range 3 weeks to 8 weeks)												
8	randomised trials	not serious	not serious	not serious	not serious	none	122/2627 (4.6%)	30/1285 (2.3%)	**RR 1.68** (1.12 to 2.52)	**16 more per 1,000** (from 3 more to 35 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Treatment-emergent akathisia (follow up: range 3 weeks to 8 weeks)												
9	randomised trials	not serious	not serious	not serious	not serious	strong association	448/2880 (15.6%)	66/1412 (4.7%)	**RR 3.36** (2.48 to 4.56)	**110 more per 1,000** (from 69 more to 166 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Treatment-emergent parkinsonism (follow up: range 3 weeks to 8 weeks)												
8	randomised trials	not serious	not serious	not serious	not serious	strong association	225/2334 (9.6%)	33/1146 (2.9%)	**RR 3.34** (2.17 to 5.13)	**67 more per 1,000** (from 34 more to 119 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Use of beta-blockers medication (follow up: range 3 weeks to 6 weeks)												
4	randomised trials	not serious	not serious	serious [3]	not serious	strong association	85/1013 (8.4%)	12/555 (2.2%)	**RR 3.71** (2.04 to 6.73)	**59 more per 1,000** (from 22 more to 124 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Use of anti-Parkinson medication (follow up: range 3 weeks to 6 weeks)												
5	randomised trials	not serious	serious [1]	serious [4]	not serious	none	285/1171(24.3%)	72/709 (10.2%)	**RR 2.79** (1.63 to 4.75)	**182 more per 1,000** (from 64 more to 381more)	⊕⊕◯◯ LOW	CRITICAL
Orthostatic hypotension (follow up: range 3 weeks to 8)												
7	randomised trials	not serious	not serious	not serious	serious [2]	none	250/2107 (11.9%)	144/1100 (13.1%)	**RR 0.93** (0.76 to 1.13)	**9 fewer per 1,000** (from 17 more to 31fewer)	⊕⊕⊕◯ MODERATE	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

1. Moderate heterogeneity (I-square > 50%) was detected
2. Number of patients included in this review is less than the optimal information size
3. Use of beta-blockers medication was used as a surrogate of adverse event of akathisia
4. Use of anti-Parkinson medication was used as a surrogate of adverse event of Parkinsonism

*Criteria for GRADE quality assessments: 1) risk of bias: outcomes reported by trials with randomization or double-blinding were rated “not serious”. Outcomes reported by trials using randomization methods suffer from high risk of bias or single-blinding method were rated “serious”. Outcomes reported by trials without randomization or blinding design were rated “very serious”;

2) Inconsistency: I^2 statistic was used as the main statistic to measure consistency for outcomes in this study. Outcomes with I^2 below 50%, between 50% and 75%, and above 75% were rated “not serious”, “serious” and “very serious”, respectively;

3) Indirectness: outcomes without any indirectness in study population, intervention or outcome measurements were rated as “not serious”. Outcomes with only indirectness detected in outcome measurements were rated “serious”. Outcomes with indirectness detected in both outcome measurements and study population were rated “very serious”;

4) Imprecision: Optimal information size was calculated using online calculator (http://www.stat.ubc.ca/~rollin/stats/ssize/b2.html). Outcomes with the number of included patients not less than optimal information size were graded “not serious”. Outcomes with the number of included patient with less than optimal information size were graded “serious”;

5) Other considerations: Dose-dependent response was assessed where possible; publication bias was assessed if more than 10 studies were included; outcomes with a statistically significant risk ratio greater than 2.0 was rated “large effect” and if greater than 5.0 rated “very large effect”.

Supplementary Table 3. Summary of findings

Cariprazine compared to placebo for schizophrenia or bipolar disorder

Patient or population: schizophrenia or bipolar disorder

Setting:

Intervention: cariprazine

Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect	№ of participants	Quality of the evidence	Co
	Risk with placebo	Risk with cariprazine	(95% CI)	(studies)	(GRADE)	
Discontinuation due to AEs follow up: range 3 weeks to 8 weeks	88 per 1,000	**99 per 1,000** (68 to 146)	**RR 1.13** (0.77 to 1.66)	4324 (9 RCTs)	⊕⊕◯◯ LOW [1,2]	
Potentially clinically significant change in weight follow up: range 3 weeks to 8 weeks	23 per 1,000	**39 per 1,000** (26 to 59)	**RR 1.68** (1.12 to 2.52)	3912 (8 RCTs)	⊕⊕⊕⊕ HIGH	
Treatment-emergent akathisia follow up: range 3 weeks to 8 weeks	47 per 1,000	**157 per 1,000** (116 to 213)	**RR 3.36** (2.48 to 4.56)	4292 (9 RCTs)	⊕⊕⊕⊕ HIGH	
Treatment-emergent parkinsonism follow up: range 3 weeks to 8 weeks	29 per 1,000	**96 per 1,000** (62 to 148)	**RR 3.34** (2.17 to 5.13)	3480 (8 RCTs)	⊕⊕⊕⊕ HIGH	
Use of beta-blockers medication follow up: range 3 weeks to 6 weeks	22 per 1,000	**80 per 1,000** (44 to 146)	**RR 3.71** (2.04 to 6.73)	1568 (4 RCTs)	⊕⊕⊕⊕ HIGH [3]	
Use of anti-Parkinson medication follow up: range 3 weeks to 6 weeks	102 per 1,000	**283 per 1,000** (166 to 482)	**RR 2.79** (1.63 to 4.75)	1880 (5 RCTs)	⊕⊕◯◯ LOW [1,4]	
Orthostatic hypotension follow up: range 3 weeks to 8	131 per 1,000	**122 per 1,000** (99 to 148)	**RR 0.93** (0.76 to 1.13)	3207 (7 RCTs)	⊕⊕⊕◯ MODERATE [2]	

CI).

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to that of the estimate of the effect

different

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

1. Moderate heterogeneity (I-square > 50%) was detected
2. Number of patients included in this review is less than the optimal information size
3. Use of beta-blockers medication was used as a surrogate of adverse event of akathisia
4. Use of anti-Parkinson medication was used as a surrogate of adverse event of Parkinsonism

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Supplementary Table 4. Meta-analysis of other outcomes, including discontinuation and safety/tolerability outcomes

Outcome		No. of studies	RR/Mean difference (95%CI)	Heterogeneity
Discontinuation	All-cause	9	0.99 (0.87, 1.13)	P=0.04, I^2=50%
	Due to withdrawal of consent	8	1.27 (1.03, 1.56)	P=0.76, I^2=0%
	Due to insufficient response	8	0.64 (0.50, 0.82)	P=0.25, I^2=22%
	Due to SAE	5	1.32 (0.37, 4.67)	P=0.07, I^2=54%
	Due to loss of follow-up	5	1.61 (0.82, 3.16)	P=0.92, I^2=0%
	Due to protocol violation	5	1.22 (0.66, 2.25)	P=0.63, I^2=0%
	Due to mania	3	0.55 (0.24, 1.28)	P=0.80, I^2=0%
	Due to schizophrenia	2	0.56 (0.28, 1.11)	P=0.47, I^2=0%
TEAEs	Total	9	1.15 (1.09, 1.21)	P=0.12, I^2=37%
	Insomnia	9	1.26 (0.96, 1.65)	P=0.11, I^2=39%
	Headache	8	0.93 (0.76, 1.13)	P=0.82, I^2=0%
	Nausea	9	1.57 (1.22, 2.02)	P=0.89, I^2=0%
	Extrapyramidal disorder	8	2.49 (1.83, 3.37)	P=0.50, I^2=0%
	Vomiting	6	1.88 (1.28, 2.77)	P=0.94, I^2=0%
	Constipation	7	1.61 (1.19, 2.20)	P=0.54, I^2=0%
	Diarrhea	6	1.02 (0.55, 1.88)	P=0.04, I^2=57%
	Dizziness	5	1.64 (1.07, 2.51)	P=0.73, I^2=0%
	Dyspepsia	4	1.67 (0.96, 2.90)	P=0.23, I^2=31%
	Schizophrenia	4	0.50 (0.34, 0.74)	P=0.61, I^2=0%
	Sedation	3	1.56 (0.63, 3.90)	P=0.10, I^2=56%
	Suicidal ideation	3	0.26 (0.04, 1.73)	P=0.22, I^2=35%
	Somnolence	3	1.89 (1.19, 3.01)	P=0.44, I^2=40%
	Pyrexia	2	1.69 (0.71, 4.01)	P=0.39, I^2=0%
	Weight increased	2	2.88 (0.86, 9.63)	P=0.96, I^2=0%
	Vision blurred	2	6.79 (1.26, 36.59)	P=0.96, I^2=0%
	Anxiety	2	1.19 (0.68, 2.07)	P=0.61, I^2=0%
	Pain in extremity	2	1.19 (0.54-2.62)	P=0.36, I^2=0%
	Agitation	3	0.84 (0.49, 1.43)	P=0.82, I^2=0%
	Toothache	2	0.92 (0.25-3.43)	P=0.10, I^2=64%
	Irritability	2	0.54 (0.01-28.22)	P=0.006, I^2=86%
	Abdominal discomfort	2	1.30 (0.58-2.94)	P=0.99, I^2=0%
SAEs	Total	9	0.62 (0.42, 0.91)	P=0.69, I^2=0%
	Mania	4	0.65 (0.21, 1.97)	P=0.54, I^2=0%
	Suicidal ideation	2	0.13 (0.01, 1.28)	P=0.88, I^2=0%

Liver function	PCS change in ALT*	2	2.47 (0.50, 12.14)	P=0.33, I^2=0%
	ALT (U/L)	8	2.94 (1.38, 4.51)	P=0.12, I^2=38%
	AST (U/L)	8	1.03 (0.34, 1.72)	P=0.44, I^2=0%
	Bilirubin (total, mg/dL)	8	0.01 (-0.02, 0.04)	P=0.005, I^2=66%
	AP (U/L)	5	-0.58 (-2.13, 0.98)	P=0.11, I^2=47%
Vital signs	Pulse (bpm)	9	0.68 (0.04, 1.32)	P=0.01, I^2=60%
	Waist circumference (cm)	6	0.20 (-0.25, 0.65)	P=0.33, I^2=14%
Suicidal ideation	C-SSRS assessment	6	0.91 (0.65, 1.27)	P=0.68, I^2=0%
Medication use	benzodiazepine	6	1.03 (0.98, 1.10)	P=0.28, I^2=20%
AEs after treatment period	AEs	3	0.89 (0.56, 1.42)	P=0.23, I^2=33%
	SAEs (psychotic disorder)	3	0.18 (0.04, 0.73)	P=0.56, I^2=0%

Abbreviations: AEs, adverse events; TEAEs, treatment emergent adverse events; SAEs, serious adverse events; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AP, alkaline phosphatase; C-SSRS, Columbia-Suicide Severity Rating scale; PCS, potential clinically significant; CI, confidence interval; RR=risk ratio.

*PCS change in ALT was defined as ≥3 times upper limit of normal (ULN).

Supplementary Table 5. Subgroup analysis by cariprazine doses

Outcome	Cariprazine dose	No. of studies	RR/Mean difference (95%CI)	Heterogeneity between groups
PCS weight change	<6mg/day	7	1.39 (1.06, 1.83)	P=0.86; I^2=0%
	≥6mg/ day	4	1.46 (0.96, 2.22)	
Body weight (Kg)	<6mg/day	7	0.68 (0.47, 0.89)	P=0.61; I^2=0%
	≥6mg/day	4	0.57 (0.18, 0.95)	
Treatment-emergent akathisia	<6mg/day	7	3.01 (2.00, 4.54)	P=0.29; I^2=11.5%
	≥6mg/day	4	4.16 (2.70, 6.40)	
Treatment-emergent Parkinsonism	<6mg/day	6	2.32 (1.51, 3.57)	P=0.17; I^2=46.5%
	≥6mg/day	4	3.67 (2.24, 6.02)	
BARS mean change	<6mg/day	4	0.31 (0.22, 0.41)	P=0.75; I^2=0%
	≥6mg/day	4	0.35 (0.24, 0.47)	
SAS mean change	<6mg/day	4	0.21 (0.02, 0.40)	P=0.0010; I^2=90.8%
	≥6mg/day	4	0.53 (0.50, 0.56)	

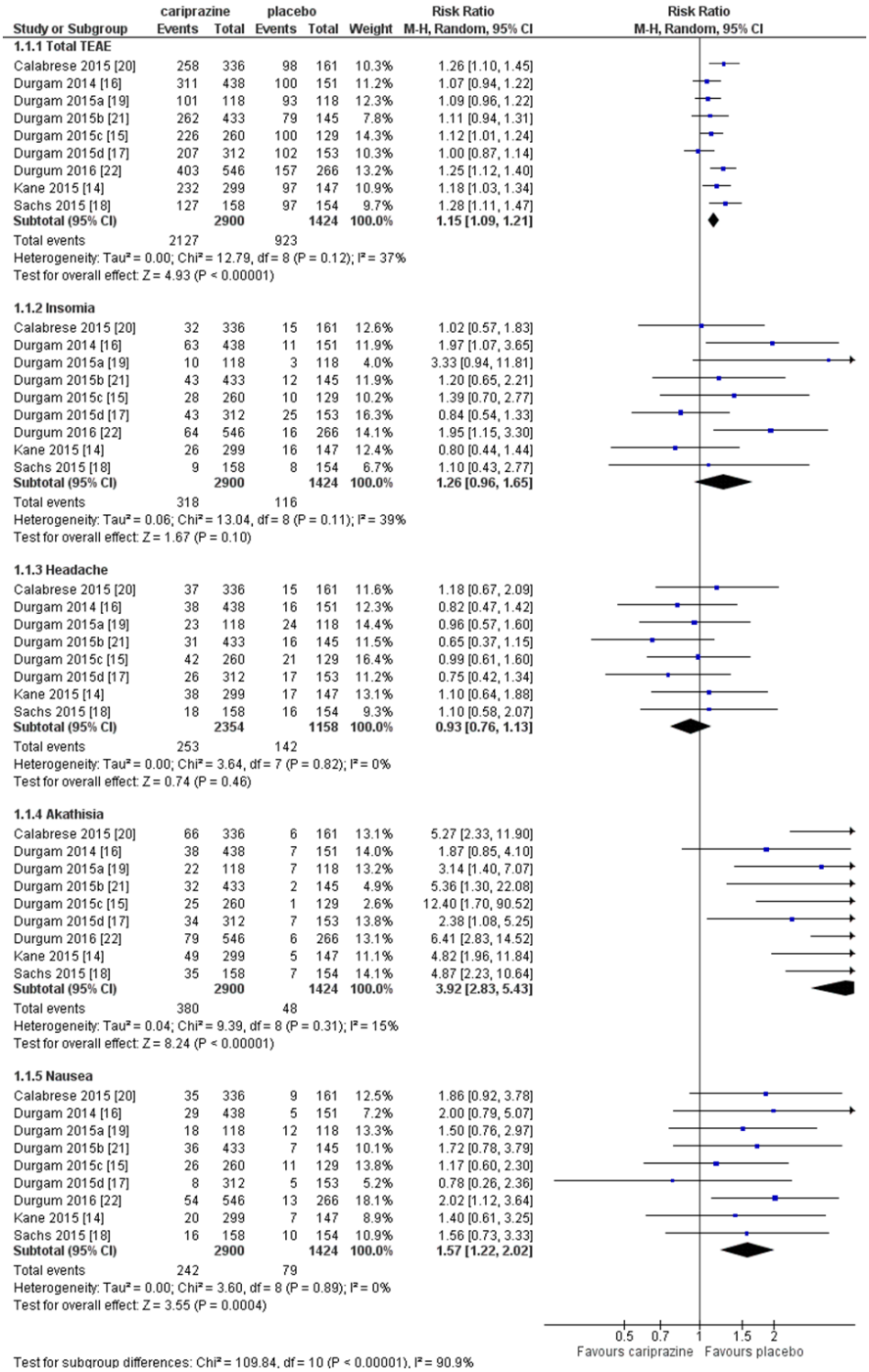
Abbreviations: PCS, potentially clinically significant; RR, risk ratio; CI, confidence interval; BARS, Barnes Akathisia Rating Scale; SAS, Simpson-Angus Scale**.**

Supplementary Table 6. Subgroup analysis by treatment indication

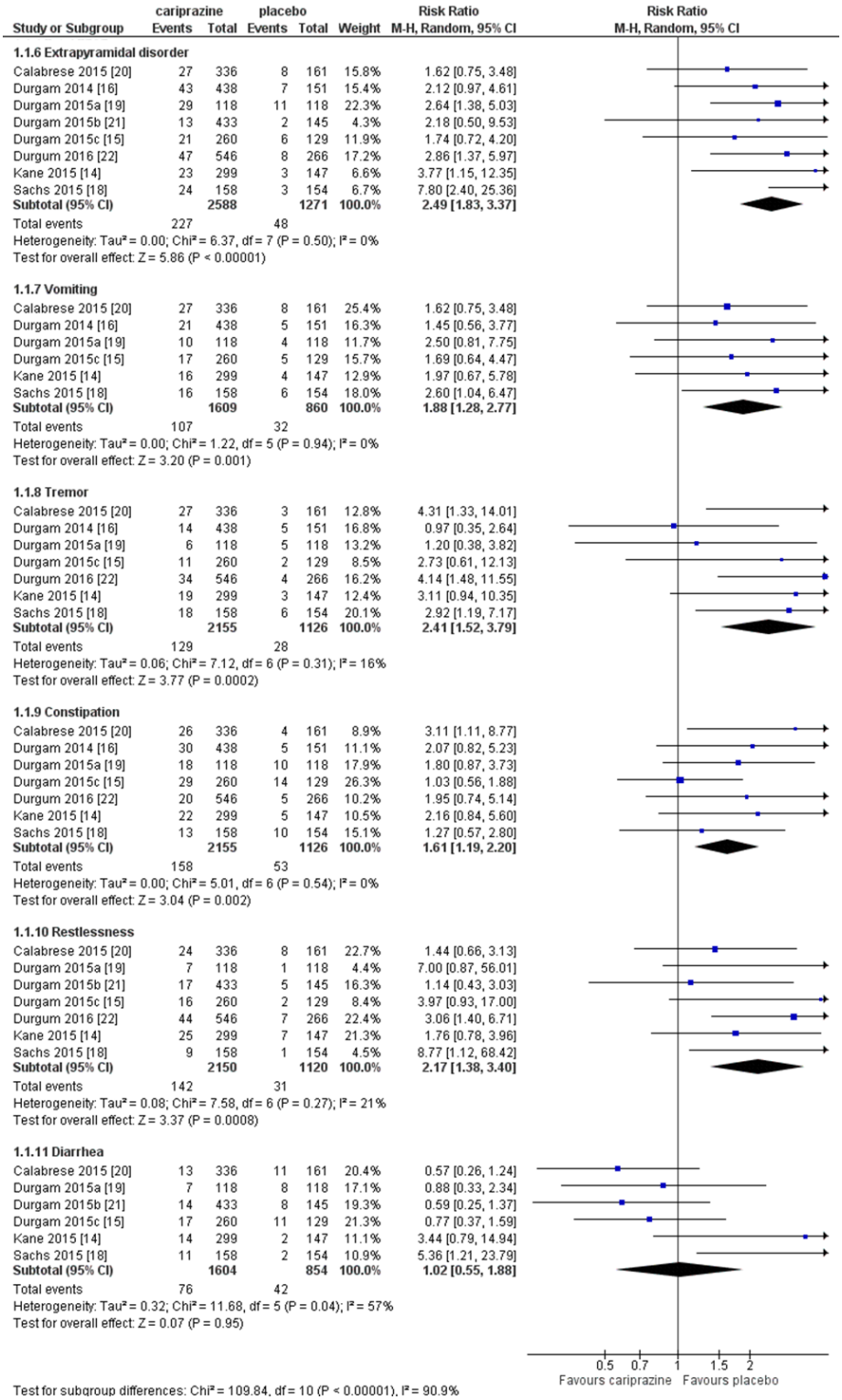
Outcome	Indication	No. of studies	RR/Mean difference (95%CI)	Heterogeneity between groups
PCS weight change	Schizophrenia	3	2.34 (1.33, 4.11)	P=0.17; I^2=46.3%
	Bipolar I mania	3	1.02 (0.36, 2.91)	
Body weight (Kg)	Schizophrenia	4	0.66 (0.35, 0.97)	P=0.17; I^2=48.1%
	Bipolar I mania	3	0.34 (0.02, 0.67)	
Treatment-emergent akathisia (BARS change)	Schizophrenia	4	2.58 (1.65, 4.03)	P=0.09; I^2=66.0%
	Bipolar I mania	3	4.49 (2.86, 7.03)	
Treatment-emergent Parkinsonism (SAS change)	Schizophrenia	4	2.37 (1.55, 3.62)	P=0.01; I^2=84.1%
	Bipolar I mania	3	6.79 (3.35, 13.76)	
BARS mean change	Schizophrenia	3	0.26 (0.13, 0.39)	P=0.03; I^2=80.0%
	Bipolar I mania	2	0.50 (0.33, 0.67)	
SAS mean change	Schizophrenia	3	0.32 (0.29, 0.36)	P=0.0010; I^2=90.8%
	Bipolar I mania	2	0.76 (0.50, 1.01)	

Abbreviations: PCS, potential clinically significant; RR, risk ratio; CI, confidence interval; BARS, Barnes Akathisia Rating Scale; SAS, Simpson-Angus Scale.

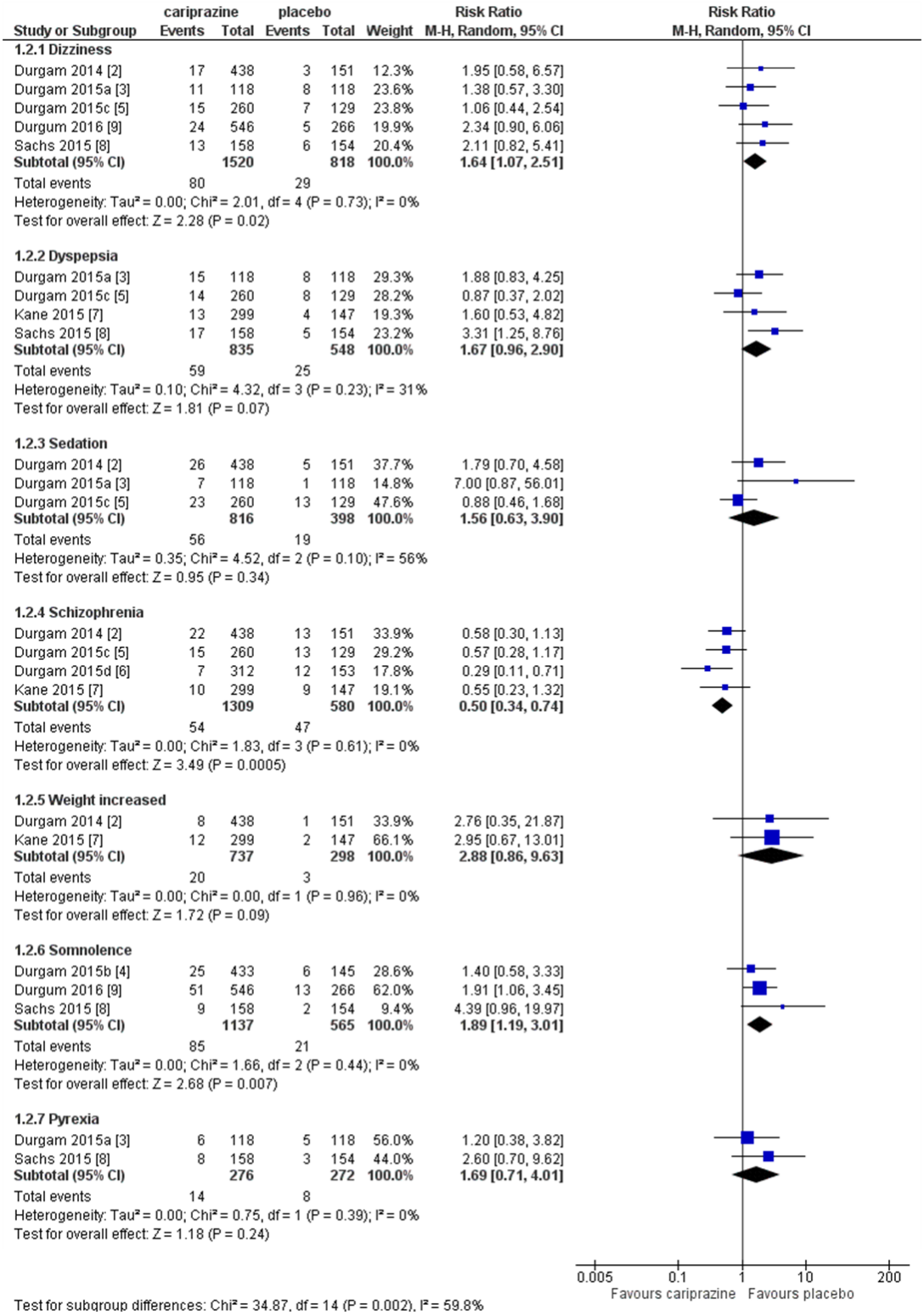
Supplementary Figure 1-1. Forest plots of all outcomes in the primary analysis: risks of treatment emergent adverse events (1)



Supplementary Figure 1-2. Forest plots of all outcomes in primary analysis: risks of treatment emergent adverse events (2)

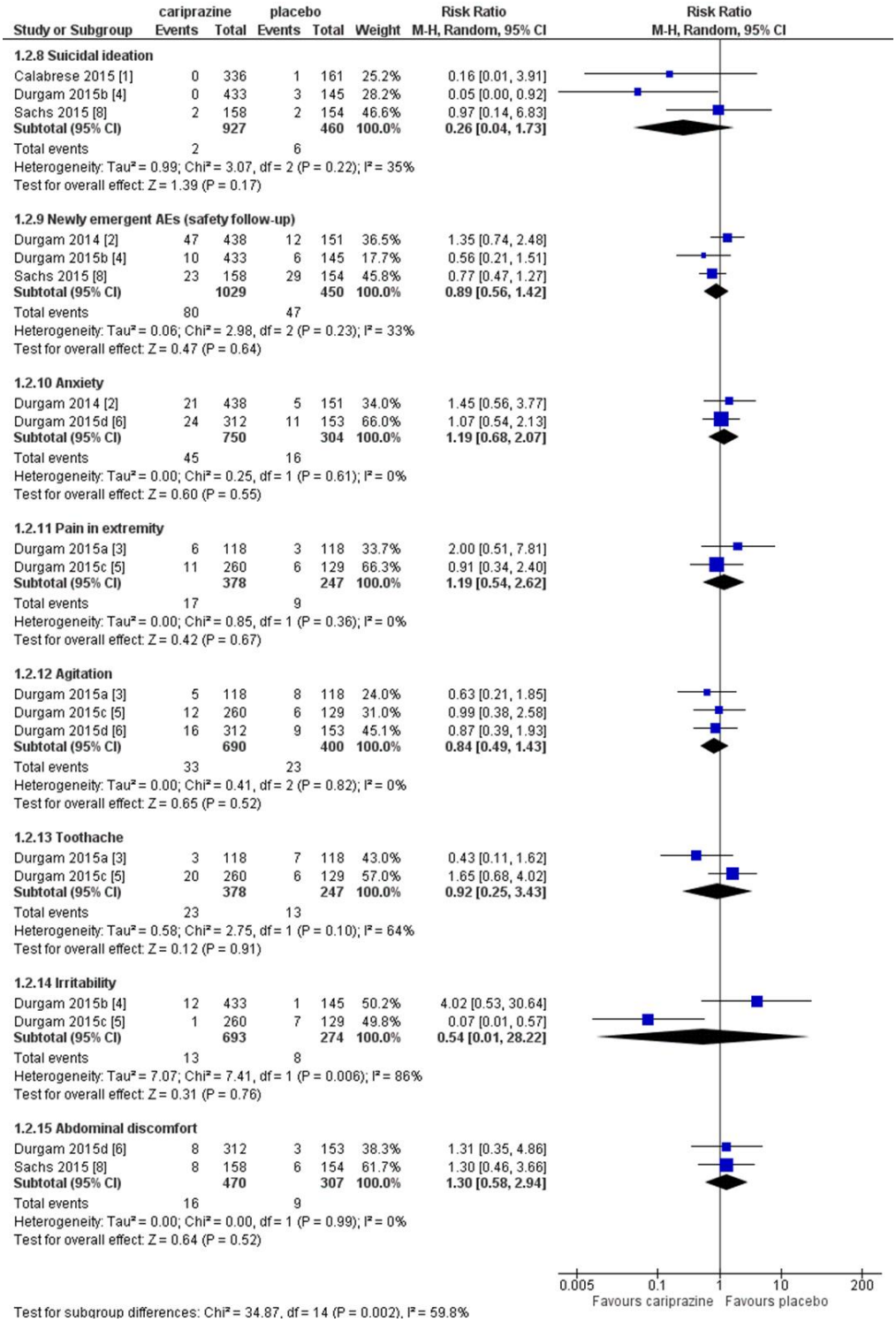


Supplementary Figure 1-3. Forest plots of all outcomes in primary analysis: risks of treatment emergent adverse events (3)

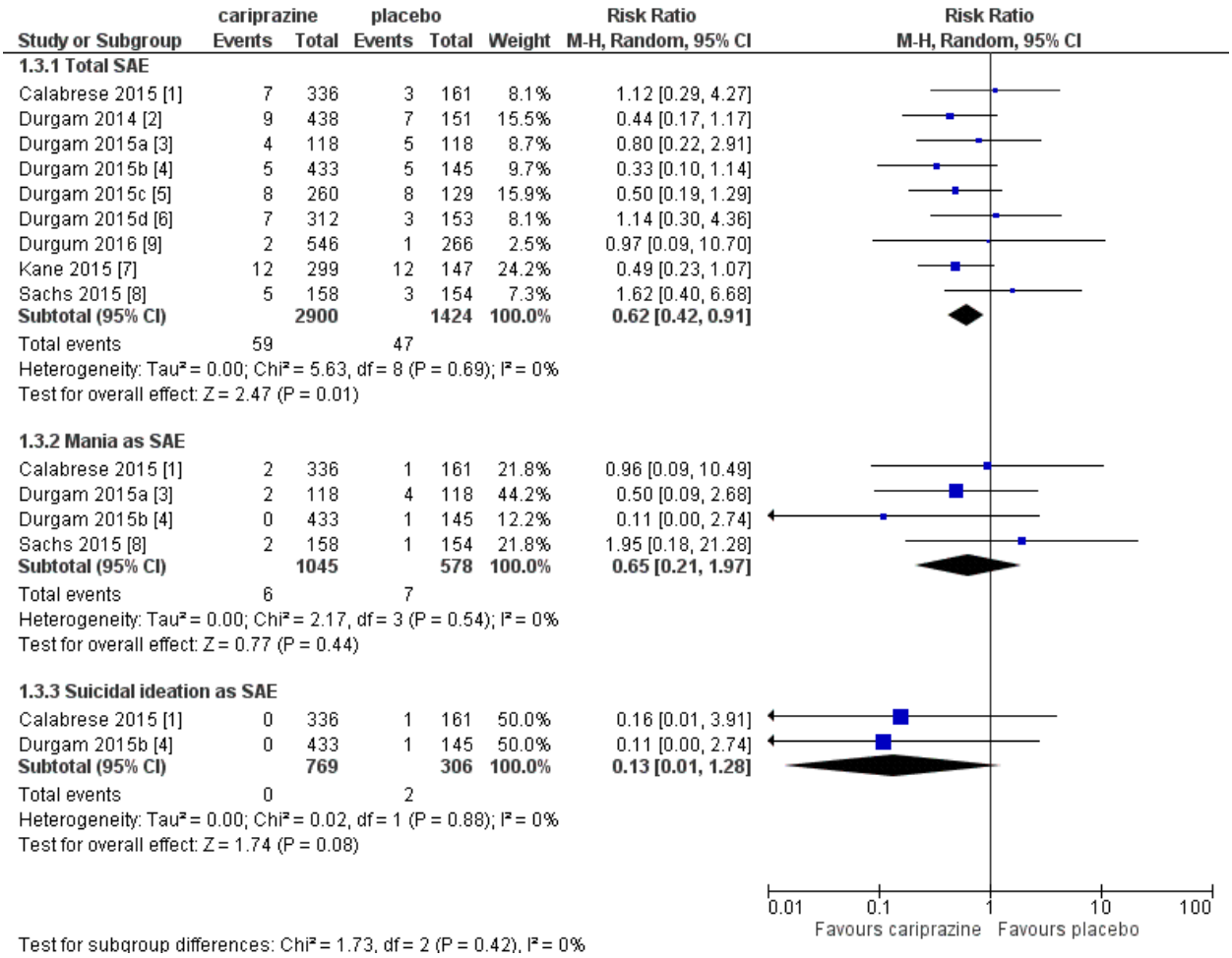


Test for subgroup differences: Chi² = 34.87, df = 14 (P = 0.002), I² = 59.8%

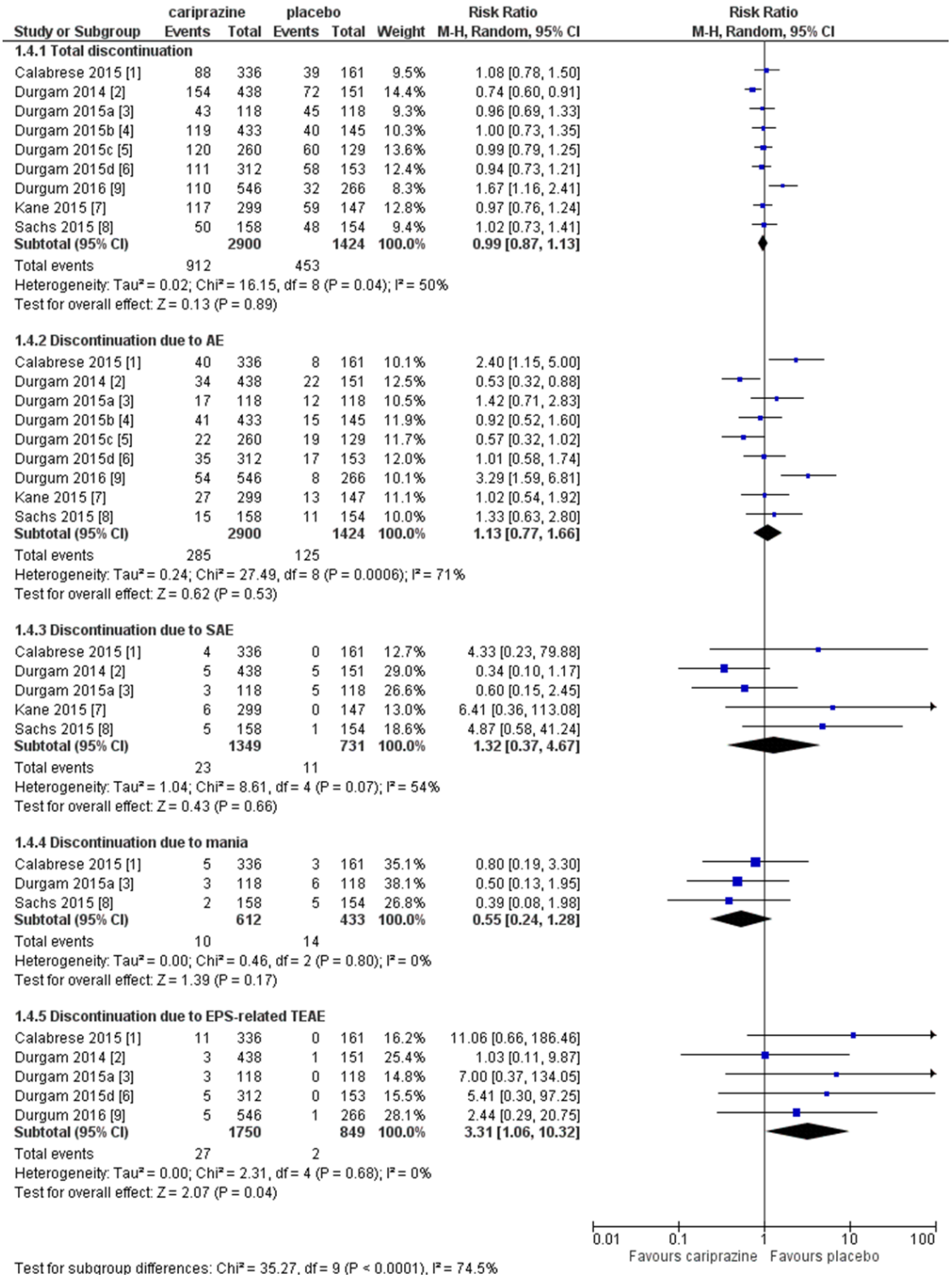
Supplementary Figure 1-4. Forest plots of all outcomes in primary analysis: risks of treatment emergent adverse events (4)



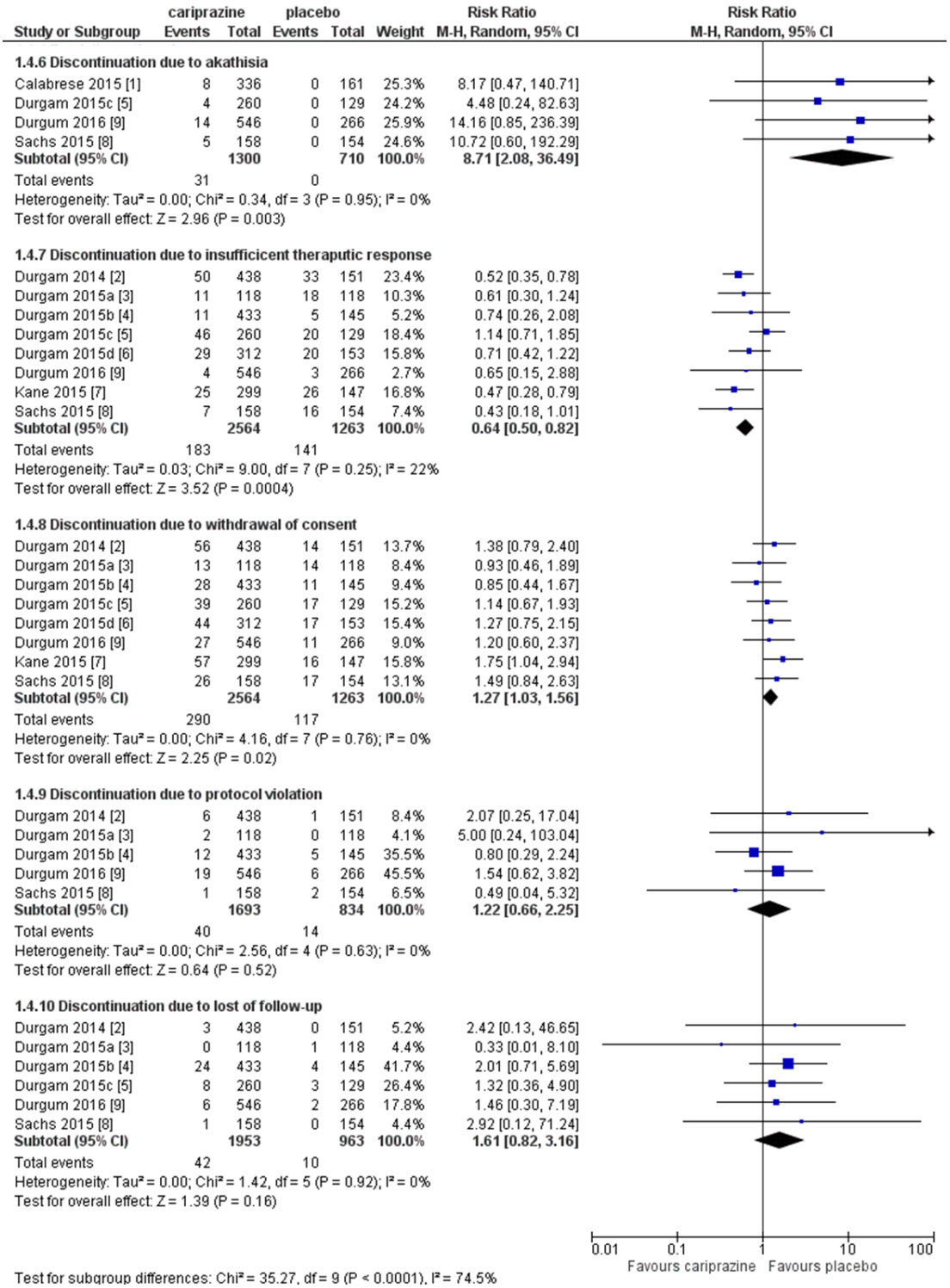
Supplementary Figure 1-5. Forest plots of all outcomes in primary analysis: risks of severe adverse events



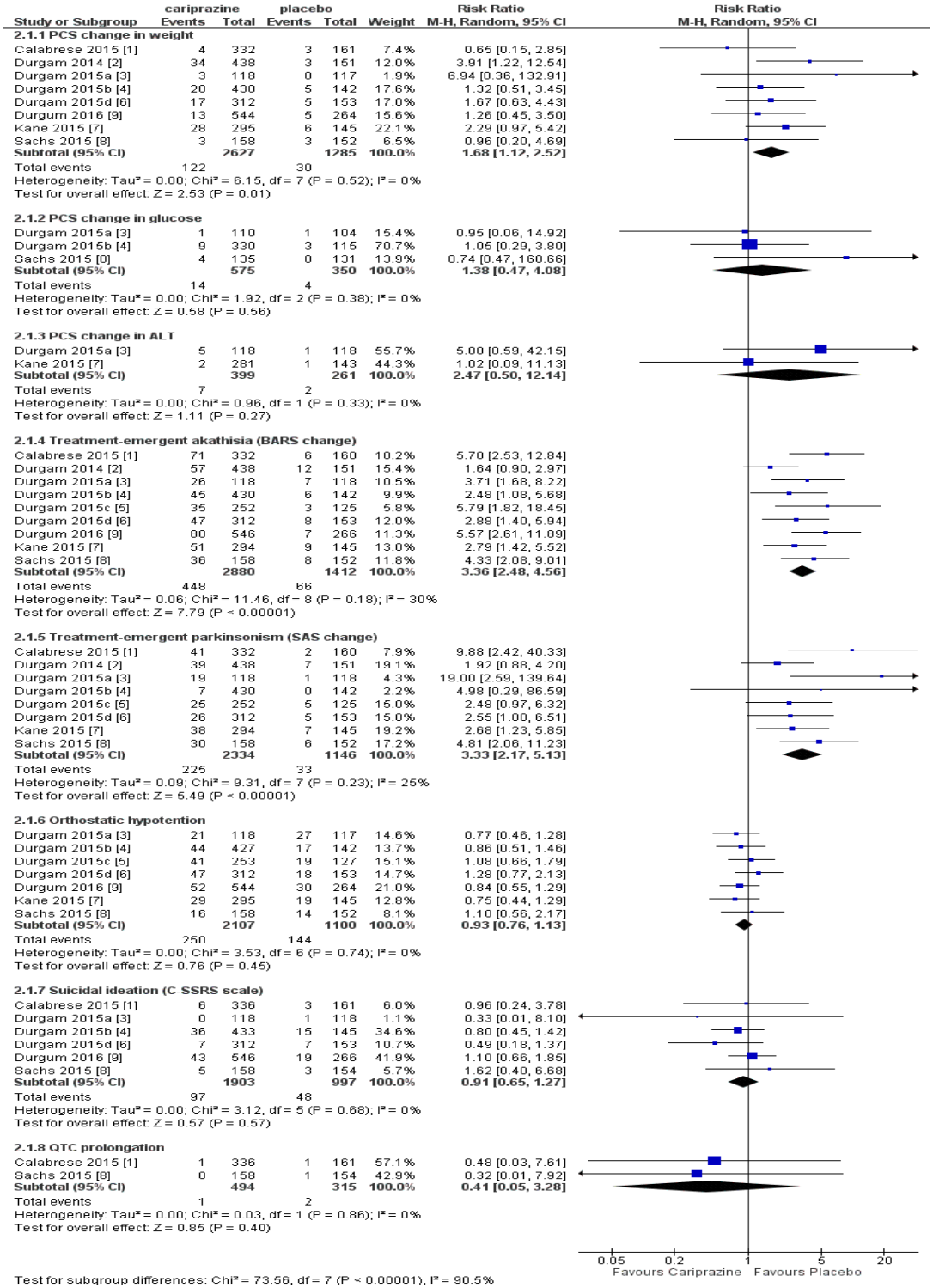
Supplementary Figure 1-6. Forest plots of all outcomes in primary analysis: risks of discontinuation of treatment (1)



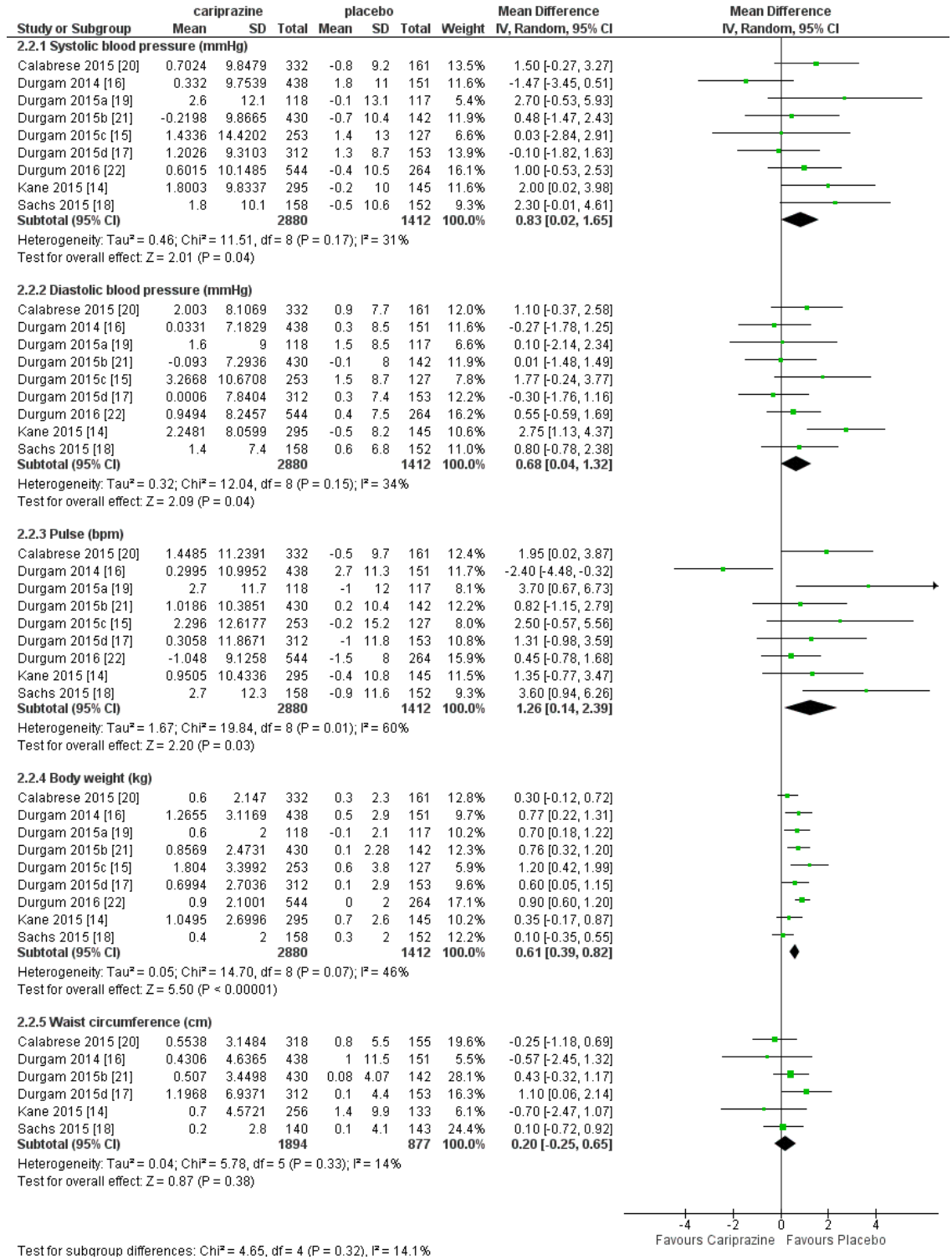
Supplementary Figure 1-7. Forest plots of all outcomes in primary analysis: risks of discontinuation of treatment (2)



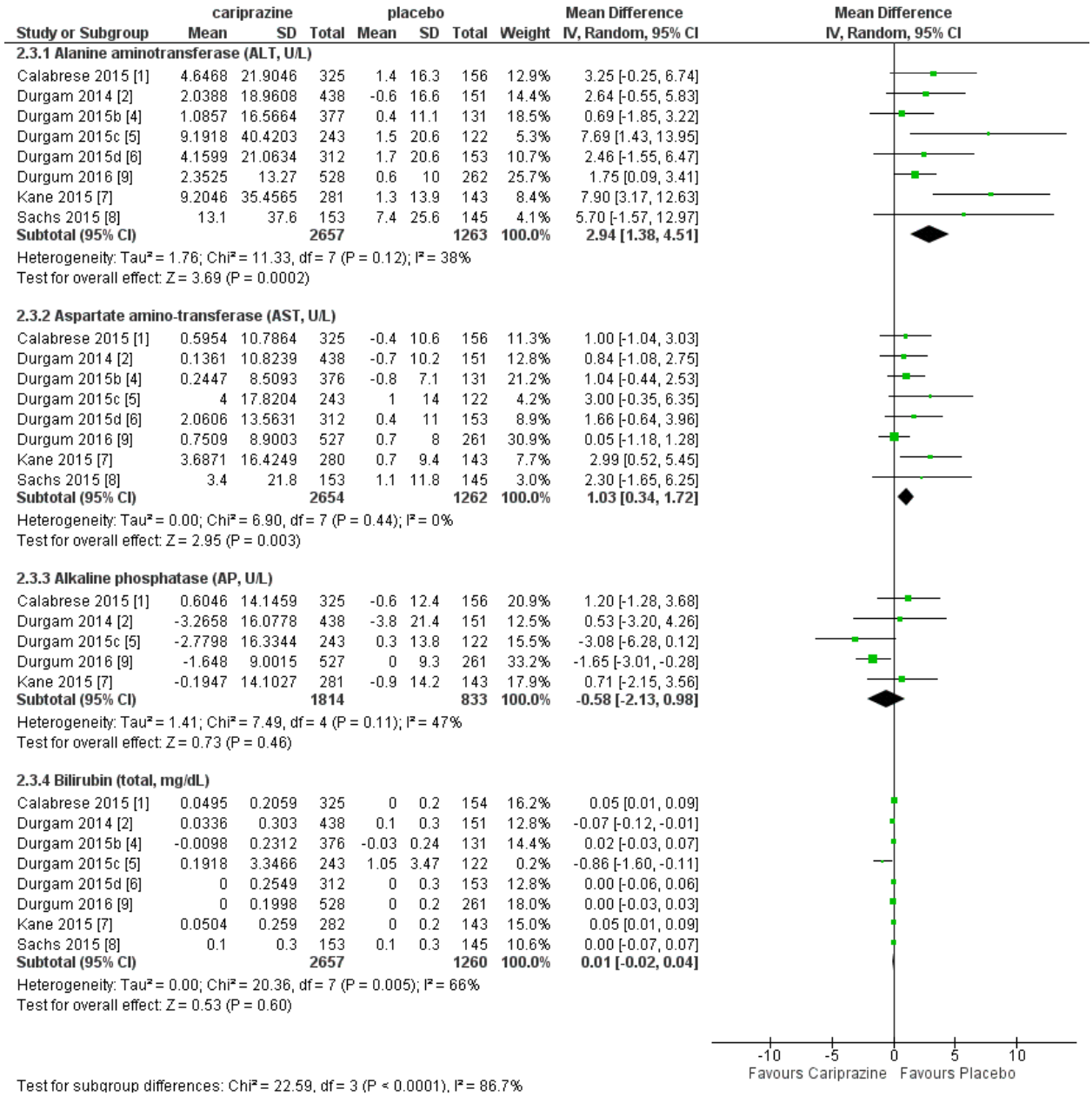
Supplementary Figure 1-8. Forest plots of all outcomes in primary analysis: risk of potentially clinically significant change of laboratory parameters



Supplementary Figure 1-9. Forest plots of all outcomes in primary analysis: mean changes from baseline in vital signs

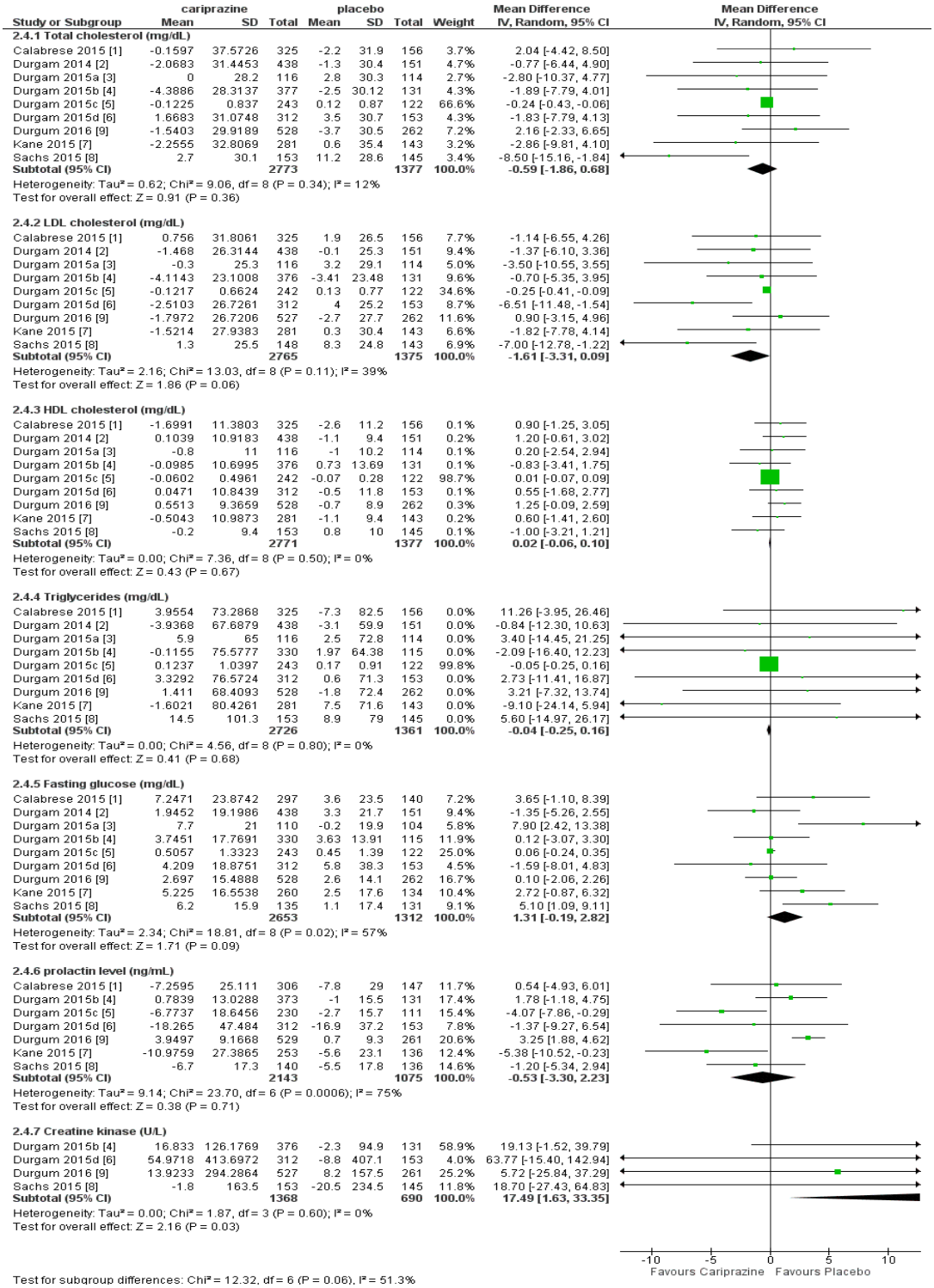


Supplementary Figure 1-10. Forest plots of all outcomes in primary analysis: mean changes from baseline in liver function parameters

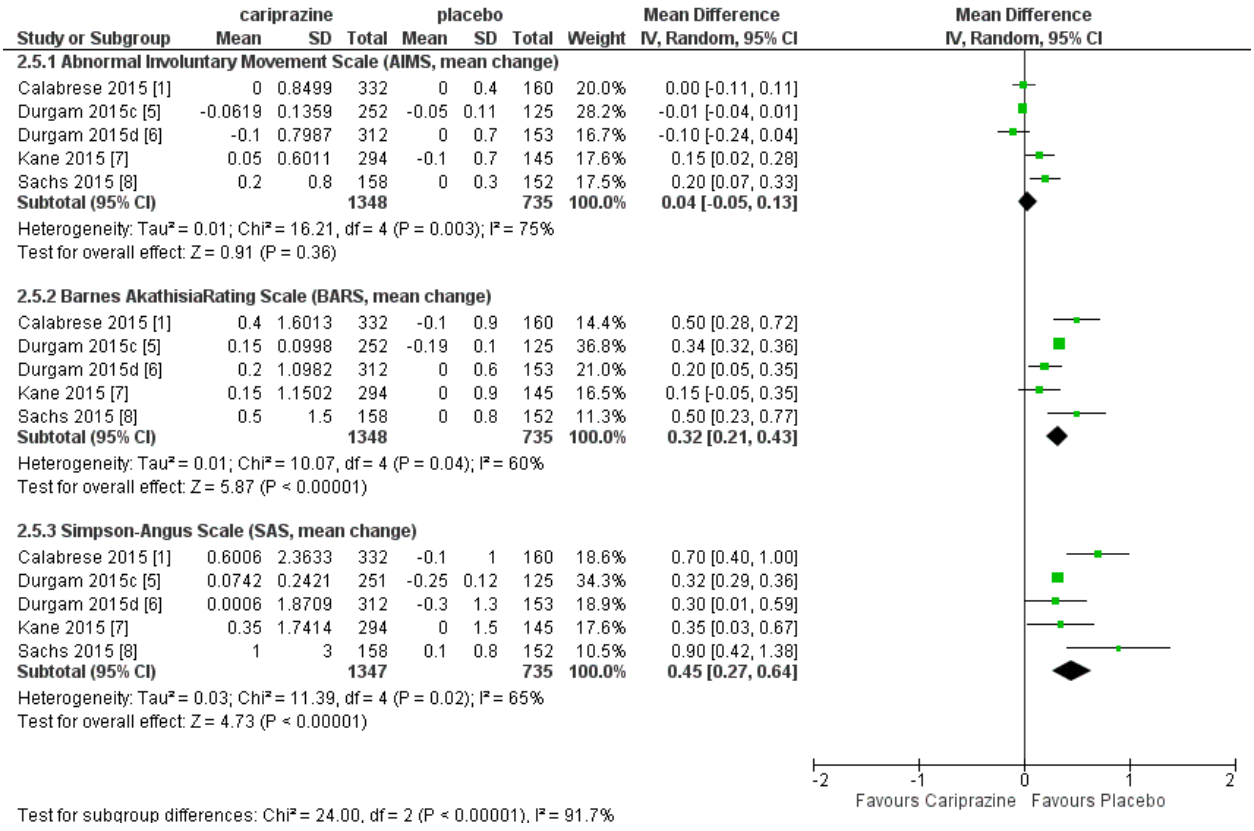


Test for subgroup differences: Chi² = 22.59, df = 3 (P < 0.0001), I² = 86.7%

Supplementary Figure 1-11. Forest plots of all outcomes in primary analysis: mean changes from baseline in metabolic parameters

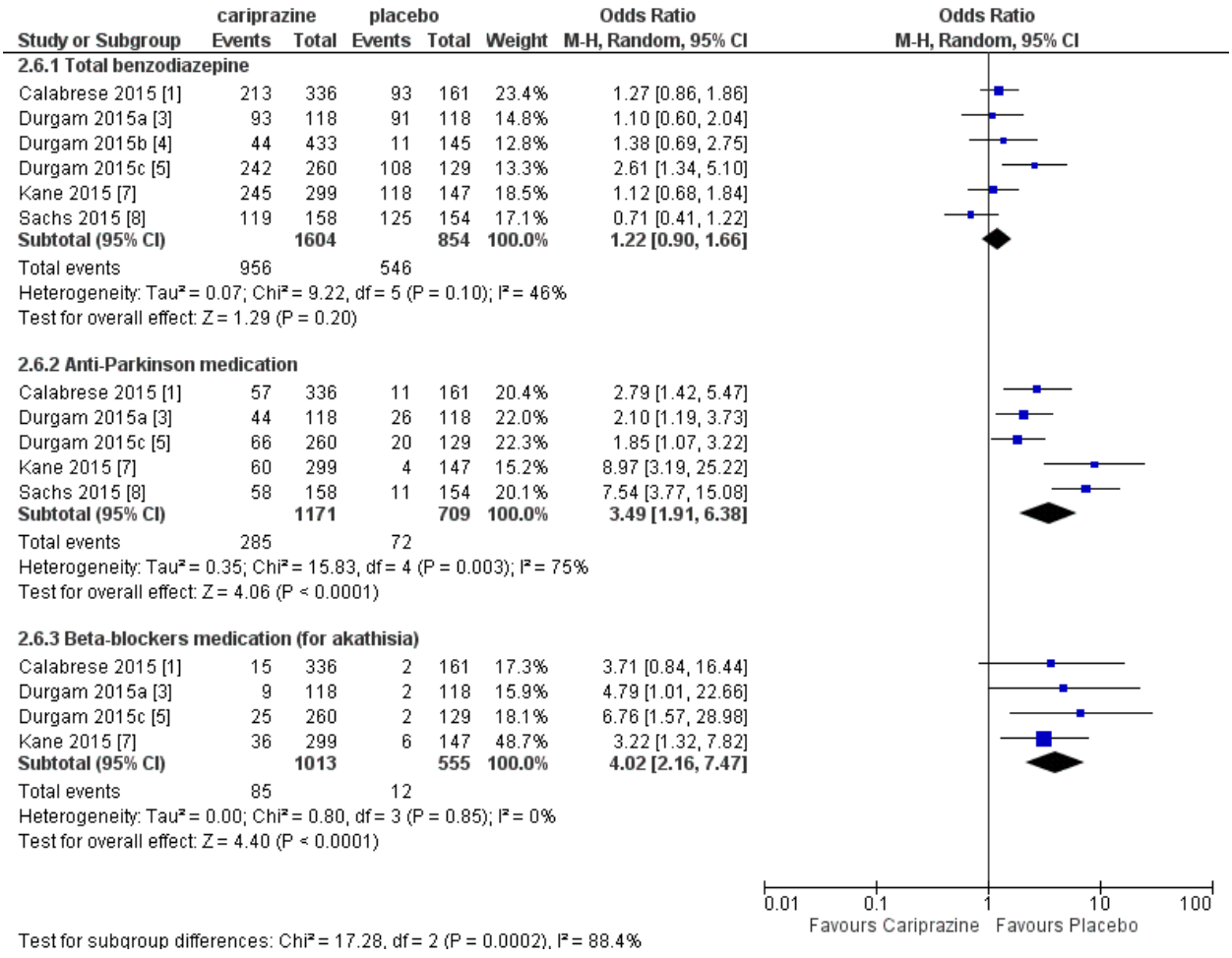


Supplementary Figure 1-12. Forest plots of all outcomes in primary analysis: mean changes from baseline in psychiatric scales



Test for subgroup differences: Chi² = 24.00, df = 2 (P < 0.00001), I² = 91.7%

Supplementary Figure 1-13. Forest plots of all outcomes in primary analysis: risks of use of rescue medication for adverse events



Abbreviations: EPS, extrapyramidal side effects; AIMS, Abnormal Involuntary Movement Scale; AE, adverse event; TEAE, treatment emergent adverse event; SAE, serious adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AP, alkaline phosphatase; C-SSRS, Columbia-Suicide Severity Rating scale; PCS, potential clinically significant; CI, confidence interval; RR, risk ratio; BARS, Barnes Akathisia Rating Scale; SAS, Simpson-Angus Scale; LDL, low-density lipoprotein; HDL, high-density lipoprotein; SBP, systolic blood pressure; DBP, diastolic blood pressure.