A systematic review and meta-analysis of oral paracetamol versus combination oral analgesics for acute musculoskeletal injuries

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1/5/19

Background

- Acute MSK injuries are common
- Management: RICE + analgesia
- Commonly used analgesics
  - paracetamol / NSAIDs / opioids

Background – which agent to use?

- Prescribing practice varies widely
- Jones et al. Cochrane review
  - compared NSAIDs with other oral analgesics for soft tissue injuries
  - 16 trials ; > 2000 patients
  - "no clinically important difference in analgesic efficacy between NSAIDs and other oral analgesic agents"
- What about combining agents?

Aim

- compare paracetamol alone vs in combination with other oral analgesics for treating acute MSK injuries
  - Analgesic efficacy
  - Side effect profile

METHODS

- Inclusion criteria
  - RCTs comparing paracetamol monotherapy with combination oral analgesics for acute MSK injuries
- Exclusions
  - Chronic back pain, c-spine injury, overuse injuries, DOMS, primary inflammatory conditions

METHODS

- Study registered with PROSPERO (CRD42019123040)
- Systematic search
  - MEDLINE (via PubMed), EMBASE and Cochrane databases

(((musculoskeletal injury OR trauma OR peripheral injury OR limb injury)) AND (analgesic OR paracetamol OR acetaminophen OR NSAID OR Opioid)) AND (Paracetamol OR Acetaminophen OR Paracetamol monotherapy OR Paracetamol only OR Paracetamol alone OR Acetaminophen monotherapy OR Acetaminophen only OR Acetaminophen alone)

Edit Clear

Builder

	All Fields	musculoskeletal injury OR trauma OR peripheral injury OR limb injury	Show index list
AND	All Fields	analgesic OR paracetamol OR acetaminophen OR NSAID OR Opioid	Show index list
AND	All Fields	Paracetamol OR Acetaminophen OR Paracetamol monotherapy OR Paracetamol only OR	Show index list
OR	All Fields		Show index list
AND	All Fields		Show index list

Search or Add to history

METHODS

- Clinical Outcome Measures

  - Difference in pain score (VAS: 0-100mm)
    - at rest / on movement
    - t = 2h, 24h, 72h
    - 13mm = clinically significant

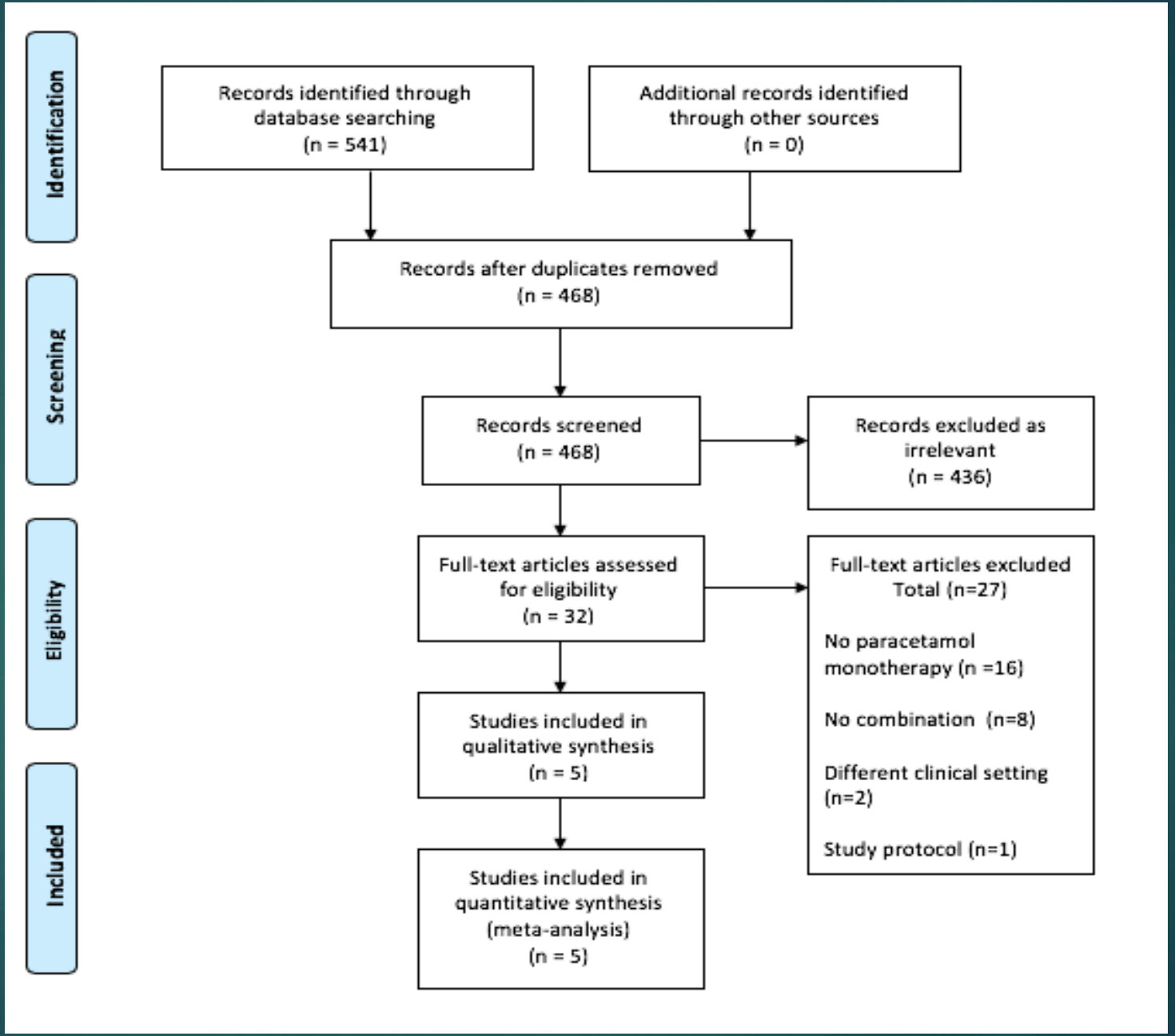
  - Need for additional analgesia

  - Adverse Events

METHODS

- Independent extraction of data – standardised forms
- Discrepancies resolved through discussion / 3rd reviewer
- Risk of Bias – Cochrane Risk of Bias Assessment Tool
- Statistical analysis : - Revman software
  - I^2 test for heterogeneity

RESULTS


Identification
Screening
Eligibility
Included
Records identified through database searching (n = 541)
Additional records identified through other sources (n = 0)
Records after duplicates removed (n = 468)
Records screened (n = 468)
Records excluded as irrelevant (n = 436)
Full-text articles assessed for eligibility (n = 32)
Full-text articles excluded Total (n=27)
No paracetamol monotherapy (n =16)
No combination (n=8)
Different clinical setting (n=2)
Study protocol (n=1)
Studies included in qualitative synthesis (n = 5)
Studies included in quantitative synthesis (meta-analysis) (n = 5)

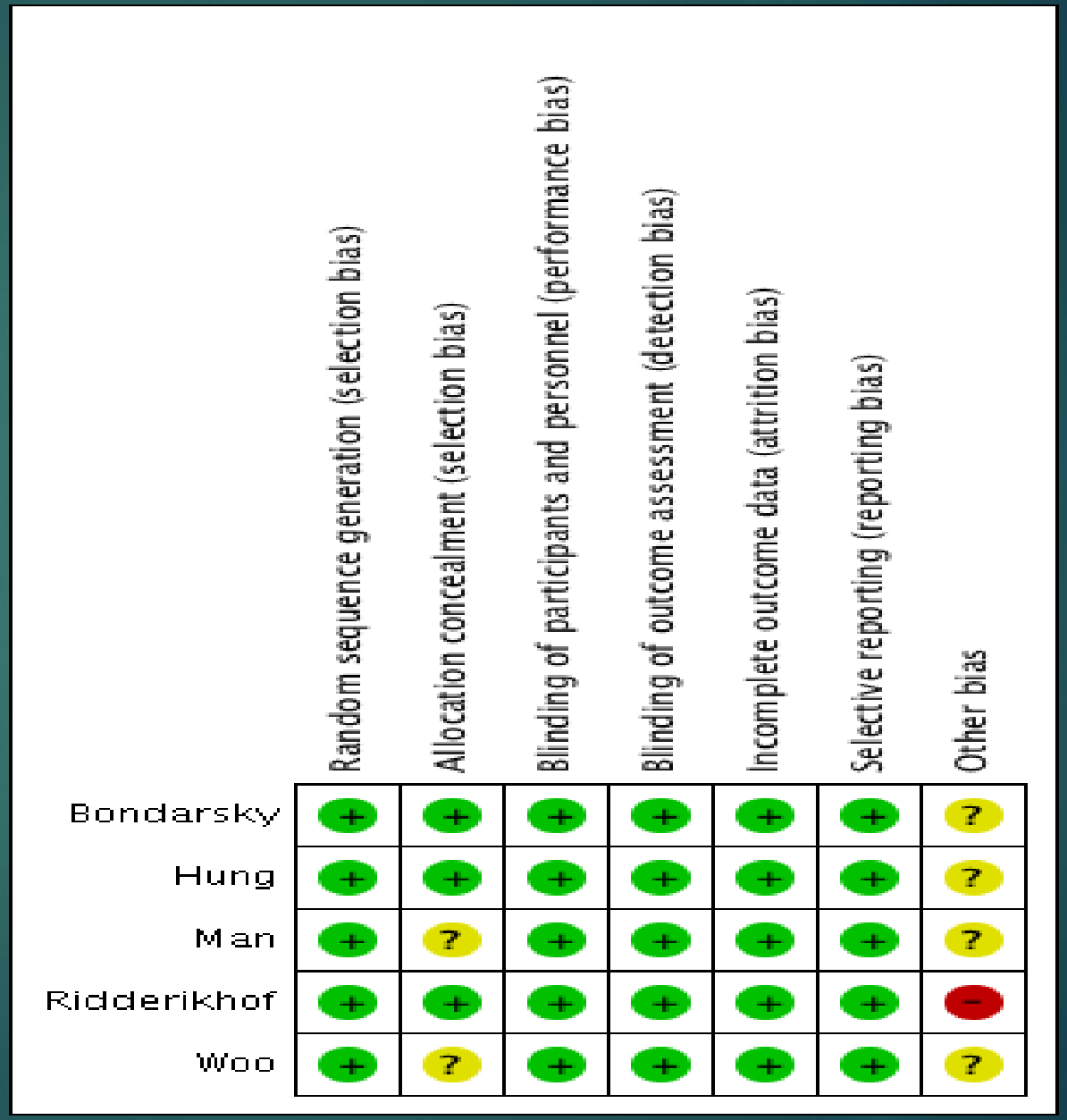
RESULTS

- Studies included in analysis: n = 5
- Total number of patients = 1135

Study	Study Site	Sample size (n)	% male	Mean Age (years)	Comparison groups
Man, 2004	1 x ED	27	55.6	36.5	1G paracetamol QID 1G paracetamol QID+25mg diclofenac TDS
Woo,2005	1x ED	160	61.9	37	1G paracetamol QID 1G paracetamol QID+25mg diclofenac TDS
Bondarsky, 2013	1 x ED	60	55	35.5	1G paracetamol 1G paracetamol+800mg ibuprofen
Hung, 2018	1 x ED	524	65.4	39	1G paracetamol QID 1G paracetamol QID+400mg ibuprofen TDS
Ridderikhof, 2018	2 x ED 2 x GP 1 x UC	364	57.1	30*	1G paracetamol QID 1G paracetamol QID+50mg diclofenac TDS

RESULTS

Cochrane Risk of Bias Assessment

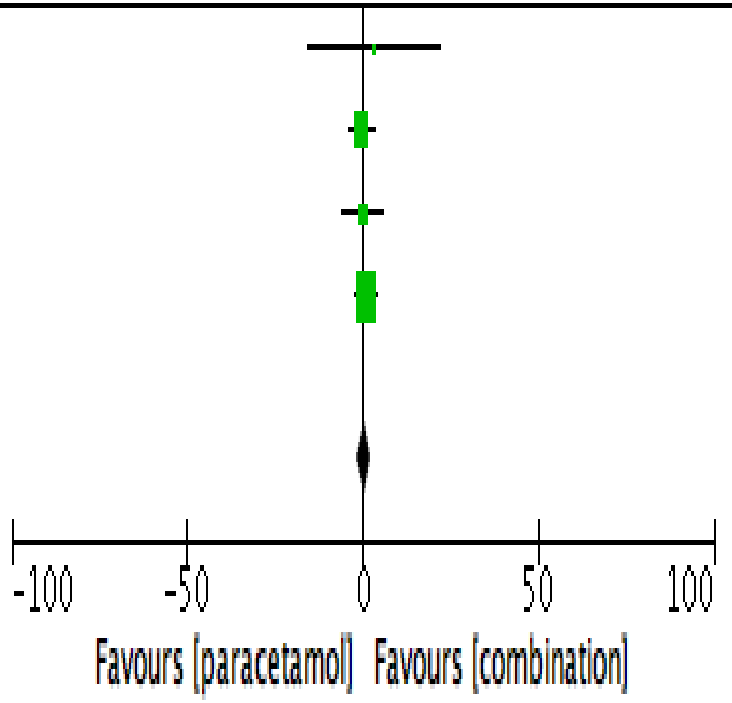


RESULTS – Pain Score (Rest)

Study or Subgroup	Paracetamol Mean	SD	Total	Combination Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Woo	-12.9	48	64	-16.1	70	92	1.4%	3.20 [-15.32, 21.72]
Ridderikhof	-12.3	18.9	167	-11.8	16.2	169	33.6%	-0.50 [-4.27, 3.27]
Man	-9.4	7.5	16	-9.5	7.1	11	15.3%	0.10 [-5.48, 5.68]
Hung	-12	16.5	219	-13	16.5	217	49.7%	1.00 [-2.10, 4.10]
Total (95% CI)			**466**			**489**	**100.0%**	**0.39 [-1.79, 2.57]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.46$, df = 3 (P = 0.93); $I^2 = 0\%$

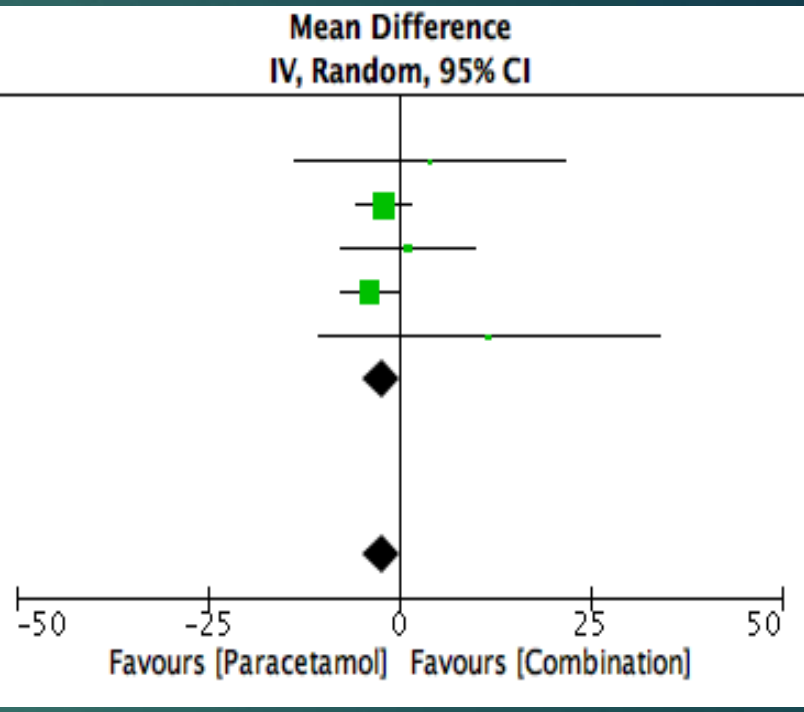
Test for overall effect: Z = 0.35 (P = 0.73)



- No difference in reduction in pain score at 2 hours

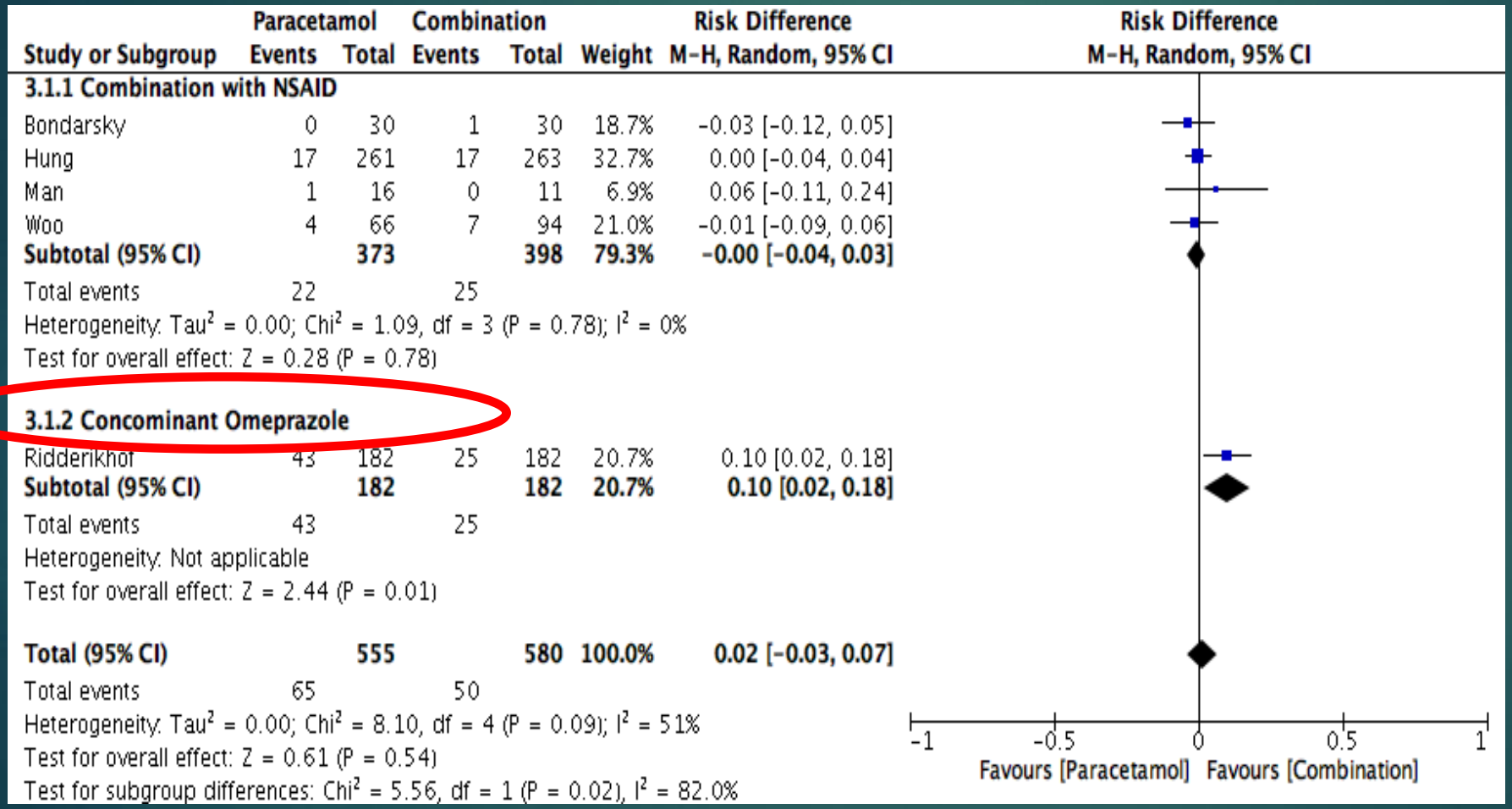
RESULTS – Pain Score (Activity)

Study or Subgroup	Paracetamol Mean	SD	Total	Combination Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.2.1 Combination with NSAID								
Bondarsky	-17	33.5	30	-21	36	30	1.9%	4.00 [-13.60, 21.60]
Hung	-17	16.5	219	-15	20.7	217	47.1%	-2.00 [-5.52, 1.52]
Man	-13.3	11.6	16	-14.5	11.1	11	7.7%	1.20 [-7.48, 9.88]
Ridderikhof	-17.2	19.6	167	-13.3	14.8	169	42.1%	-3.90 [-7.62, -0.18]
Woo	-7.6	57.9	64	-19.3	84.3	92	1.2%	11.70 [-10.61, 34.01]
Subtotal (95% CI)			**496**			**519**	**100.0%**	**-2.28 [-4.69, 0.13]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.37$, df = 4 (P = 0.50); $I^2 = 0\%$								
Test for overall effect: Z = 1.85 (P = 0.06)								
Total (95% CI)			**496**			**519**	**100.0%**	**-2.28 [-4.69, 0.13]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.37$, df = 4 (P = 0.50); $I^2 = 0\%$								
Test for overall effect: Z = 1.85 (P = 0.06)								
Test for subgroup differences: Not applicable								



- Greatest reduction in pain score at 2 hours seen with paracetamol monotherapy - <13mm
- No difference in pain scores at 24 hours or 72 hours

RESULTS – Adverse Events



Study or Subgroup	Paracetamol Events	Paracetamol Total	Combination Events	Combination Total	Weight	Risk Difference M-H, Random, 95% CI
3.1.1 Combination with NSAID						
Bondarsky	0	30	1	30	18.7%	-0.03 [-0.12, 0.05]
Hung	17	261	17	263	32.7%	0.00 [-0.04, 0.04]
Man	1	16	0	11	6.9%	0.06 [-0.11, 0.24]
Woo	4	66	7	94	21.0%	-0.01 [-0.09, 0.06]
Subtotal (95% CI)		**373**		**398**	**79.3%**	**-0.00 [-0.04, 0.03]**
Total events	22		25			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.09$, df = 3 (P = 0.78); $I^2 = 0\%$						
Test for overall effect: Z = 0.28 (P = 0.78)						
3.1.2 Concominant Omeprazole						
Ridderikhof	43	182	25	182	20.7%	0.10 [0.02, 0.18]
Subtotal (95% CI)		**182**		**182**	**20.7%**	**0.10 [0.02, 0.18]**
Total events	43		25			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.44 (P = 0.01)						
Total (95% CI)		**555**		**580**	**100.0%**	**0.02 [-0.03, 0.07]**
Total events	65		50			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 8.10$, df = 4 (P = 0.09); $I^2 = 51\%$						
Test for overall effect: Z = 0.61 (P = 0.54)						
Test for subgroup differences: $Chi^2 = 5.56$, df = 1 (P = 0.02), $I^2 = 82.0\%$						

- No difference between groups at :

- 2 hours: -0.00 (-0.04, 0.03)
- 1 week: 0.02 (-0.02, 0.07)

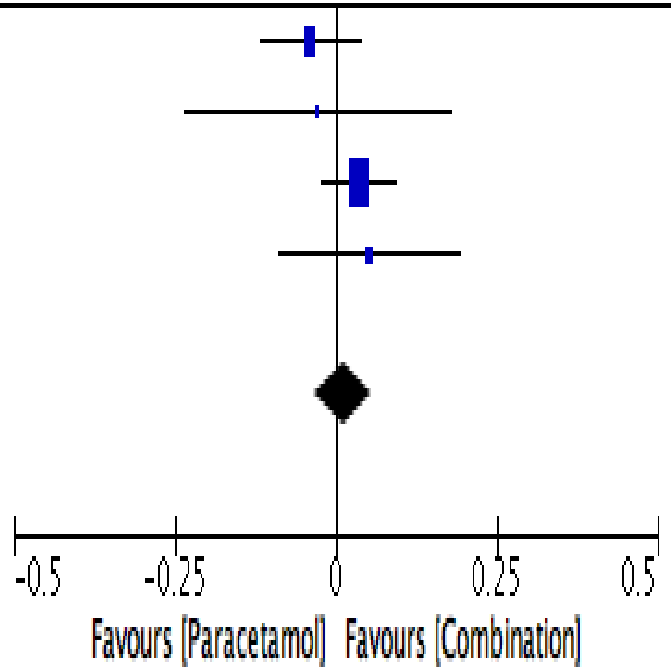
- Concominant omeprazole used in 1 study

RESULTS –Additional Analgesia

Study or Subgroup	Paracetamol Events	Paracetamol Total	Combination Events	Combination Total	Weight	Risk Difference M-H, Random, 95% CI
Hung	47	221	57	226	30.5%	-0.04 [-0.12, 0.04]
Man	1	16	1	11	4.5%	-0.03 [-0.24, 0.18]
Ridderikhof	16	167	10	169	55.1%	0.04 [-0.02, 0.09]
Woo	18	64	21	92	9.9%	0.05 [-0.09, 0.19]
Total (95% CI)		**468**		**498**	**100.0%**	**0.01 [-0.03, 0.06]**
Total events	82		89			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.09$, df = 3 ($P = 0.38$); $I^2 = 3\%$

Test for overall effect: $Z = 0.53$ ($P = 0.59$)



- No difference between groups at:

- 2hrs: -0.03 (-0.06, -0.00)
- 1week : 0.01 (-0.03, 0.06)

DISCUSSION

- No significant difference in reduction in pain score, adverse events & need for additional analgesia
- Variable findings in other clinical settings
  - post-op pain
  - dental pain
- No studies comparing paracetamol monotherapy with paracetamol + NSAID + opioid

LIMITATIONS

- Limited number of studies (n = 5)
- Minor discrepancies extrapolating data from graphs in one study
- Variation in NSAID drug and dose between studies

CONCLUSIONS

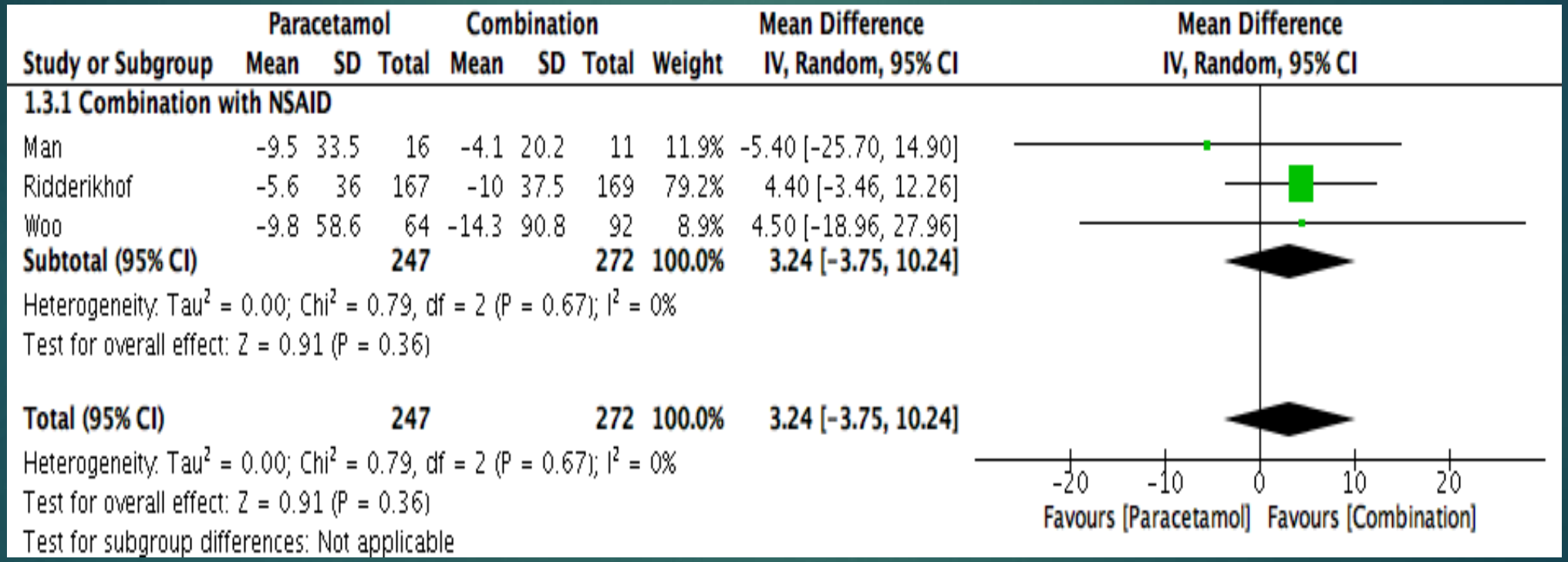
- No significant difference in analgesic efficacy between oral paracetamol and oral paracetamol + NSAID in the management of acute MSK injuries in ED
- Combining oral analgesic agents does not necessarily result in better pain relief
- Paracetamol monotherapy is a reasonable 1st line in this clinical setting

ACKNOWLEDGEMENTS

- Associate Professor Peter Jones
- Jay Gong – Clinical Pharmacist

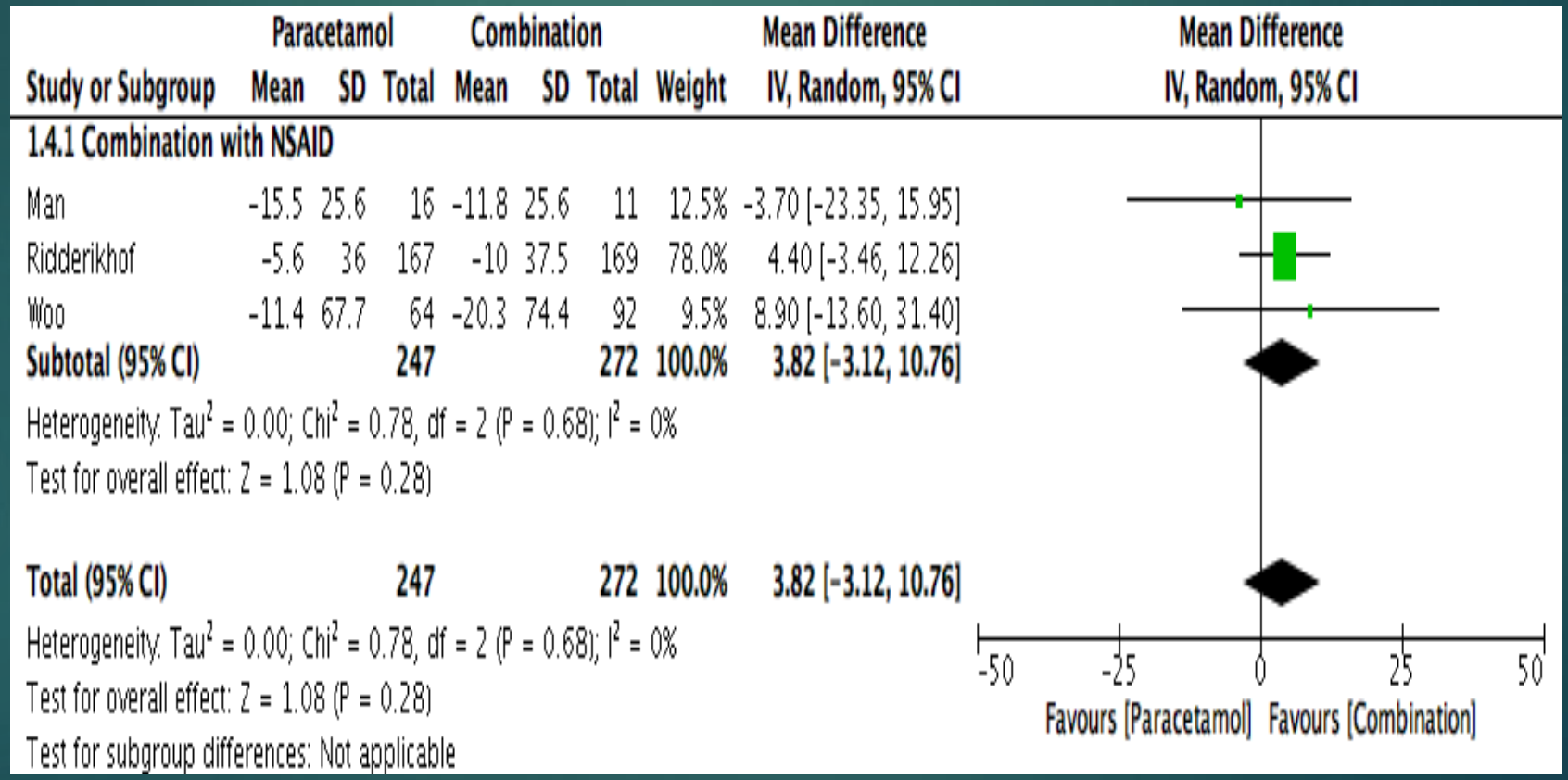
QUESTIONS

Reduction in Pain Score – 24 hours (rest)



Study or Subgroup	Paracetamol Mean	SD	Total	Combination Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.3.1 Combination with NSAID								
Man	-9.5	33.5	16	-4.1	20.2	11	11.9%	-5.40 [-25.70, 14.90]
Ridderikhof	-5.6	36	167	-10	37.5	169	79.2%	4.40 [-3.46, 12.26]
Woo	-9.8	58.6	64	-14.3	90.8	92	8.9%	4.50 [-18.96, 27.96]
Subtotal (95% CI)			**247**			**272**	**100.0%**	**3.24 [-3.75, 10.24]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.79$, df = 2 (P = 0.67); $I^2 = 0\%$								
Test for overall effect: Z = 0.91 (P = 0.36)								
Total (95% CI)			**247**			**272**	**100.0%**	**3.24 [-3.75, 10.24]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.79$, df = 2 (P = 0.67); $I^2 = 0\%$								
Test for overall effect: Z = 0.91 (P = 0.36)								
Test for subgroup differences: Not applicable								

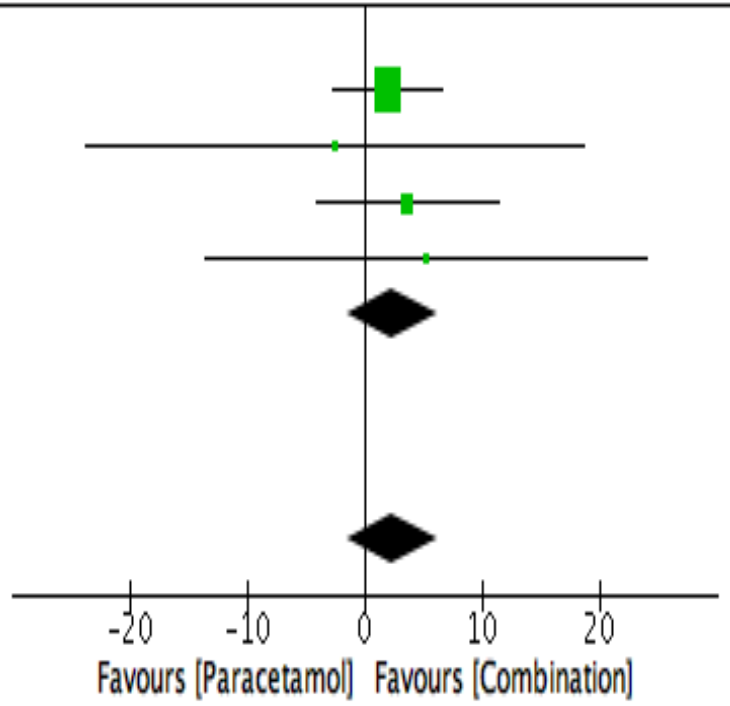
Reduction in Pain Score – 24 hours (activity)



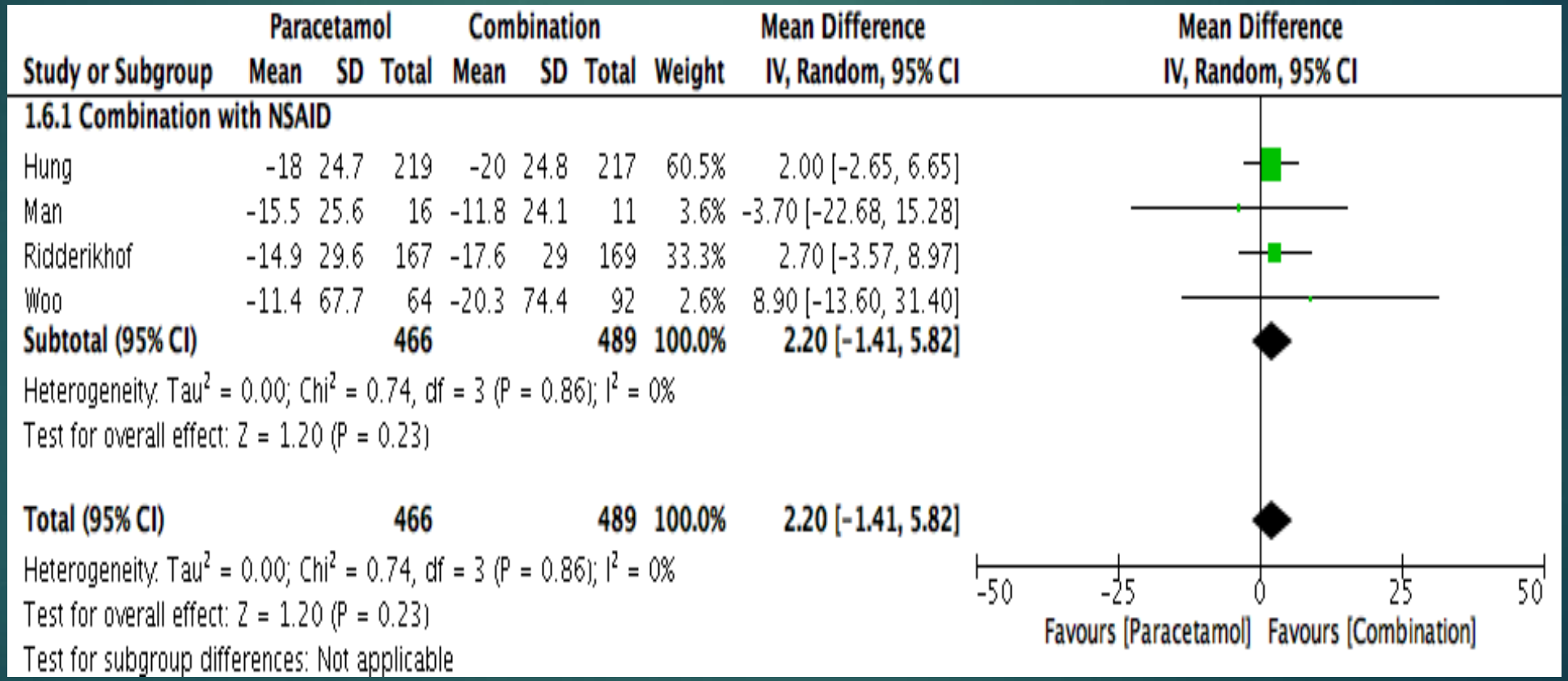
Study or Subgroup	Paracetamol Mean	SD	Total	Combination Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.4.1 Combination with NSAID								
Man	-15.5	25.6	16	-11.8	25.6	11	12.5%	-3.70 [-23.35, 15.95]
Ridderikhof	-5.6	36	167	-10	37.5	169	78.0%	4.40 [-3.46, 12.26]
Woo	-11.4	67.7	64	-20.3	74.4	92	9.5%	8.90 [-13.60, 31.40]
Subtotal (95% CI)			**247**			**272**	**100.0%**	**3.82 [-3.12, 10.76]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.78$, df = 2 (P = 0.68); $I^2 = 0\%$								
Test for overall effect: Z = 1.08 (P = 0.28)								
Total (95% CI)			**247**			**272**	**100.0%**	**3.82 [-3.12, 10.76]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.78$, df = 2 (P = 0.68); $I^2 = 0\%$								
Test for overall effect: Z = 1.08 (P = 0.28)								
Test for subgroup differences: Not applicable								

Reduction in Pain Score – 72 hours (rest)

Study or Subgroup	Paracetamol Mean	SD	Total	Combination Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.5.1 Combination with NSAID								
Hung	-18	24.7	219	-20	24.8	217	68.2%	2.00 [-2.65, 6.65]
Man	-15	34.5	16	-12.5	21.9	11	3.3%	-2.50 [-23.79, 18.79]
Ridderikhof	-18.2	36.8	167	-21.9	36	169	24.3%	3.70 [-4.09, 11.49]
Woo	-12.8	49.5	64	-18.1	70	92	4.2%	5.30 [-13.45, 24.05]
Subtotal (95% CI)			**466**			**489**	**100.0%**	**2.41 [-1.43, 6.24]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.43$, df = 3 (P = 0.93); $I^2 = 0\%$								
Test for overall effect: Z = 1.23 (P = 0.22)								
Total (95% CI)			**466**			**489**	**100.0%**	**2.41 [-1.43, 6.24]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.43$, df = 3 (P = 0.93); $I^2 = 0\%$								
Test for overall effect: Z = 1.23 (P = 0.22)								
Test for subgroup differences: Not applicable								



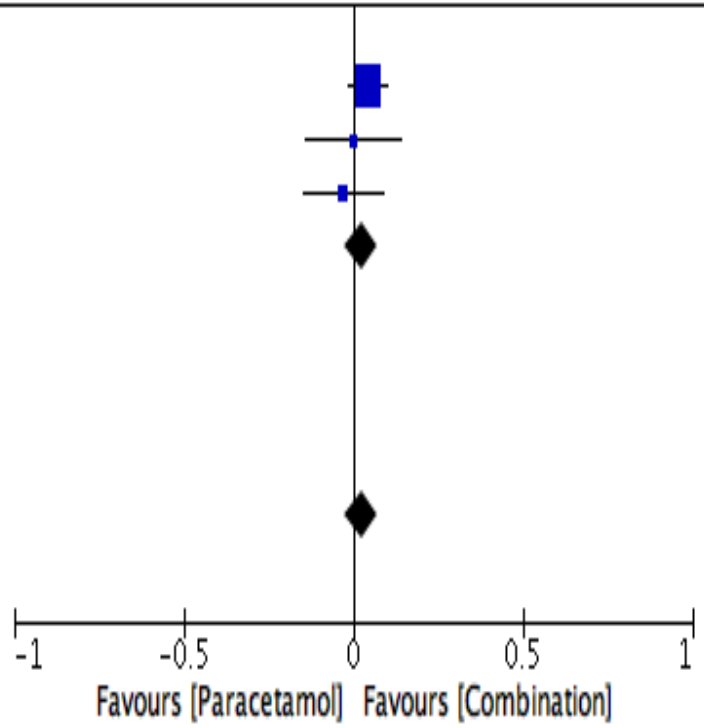
Reduction in Pain Score – 72 hours (activity)



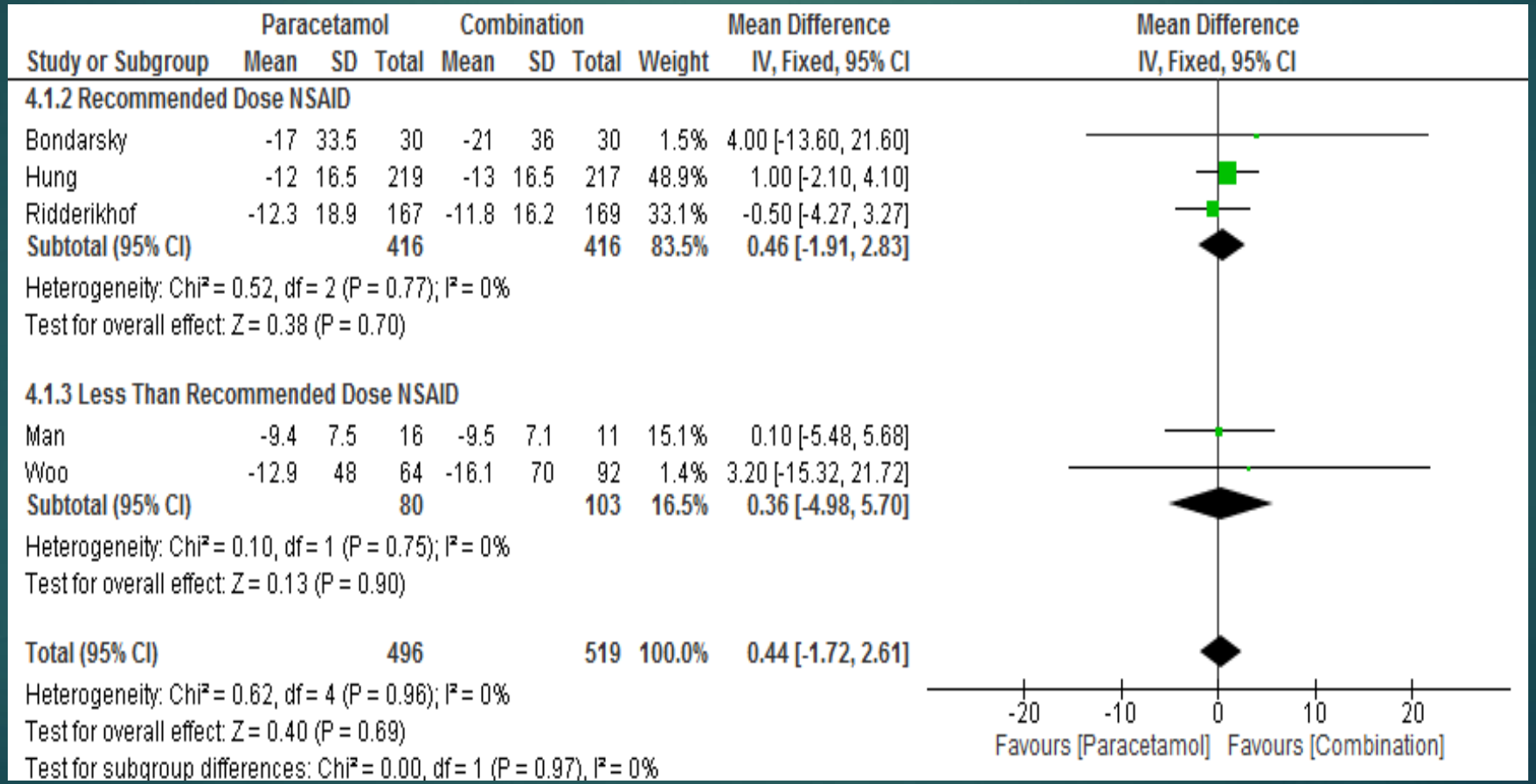
Study or Subgroup	Paracetamol Mean	SD	Total	Combination Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.6.1 Combination with NSAID								
Hung	-18	24.7	219	-20	24.8	217	60.5%	2.00 [-2.65, 6.65]
Man	-15.5	25.6	16	-11.8	24.1	11	3.6%	-3.70 [-22.68, 15.28]
Ridderikhof	-14.9	29.6	167	-17.6	29	169	33.3%	2.70 [-3.57, 8.97]
Woo	-11.4	67.7	64	-20.3	74.4	92	2.6%	8.90 [-13.60, 31.40]
Subtotal (95% CI)			**466**			**489**	**100.0%**	**2.20 [-1.41, 5.82]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.74$, df = 3 (P = 0.86); $I^2 = 0\%$								
Test for overall effect: Z = 1.20 (P = 0.23)								
Total (95% CI)			**466**			**489**	**100.0%**	**2.20 [-1.41, 5.82]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.74$, df = 3 (P = 0.86); $I^2 = 0\%$								
Test for overall effect: Z = 1.20 (P = 0.23)								
Test for subgroup differences: Not applicable								

Adverse Events – 1 week

Study or Subgroup	Paracetamol Events	Paracetamol Total	Combination Events	Combination Total	Weight	Risk Difference M-H, Random, 95% CI
3.2.1 Combination with NSAID						
Hung	41	261	30	263	69.9%	0.04 [-0.02, 0.10]
Man	0	16	0	11	12.4%	0.00 [-0.14, 0.14]
Woo	10	66	17	94	17.7%	-0.03 [-0.15, 0.09]
Subtotal (95% CI)		**343**		**368**	**100.0%**	**0.02 [-0.02, 0.07]**
Total events	51		47			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.33$, df = 2 (P = 0.51); $I^2 = 0\%$						
Test for overall effect: Z = 1.00 (P = 0.32)						
Total (95% CI)		**343**		**368**	**100.0%**	**0.02 [-0.02, 0.07]**
Total events	51		47			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.33$, df = 2 (P = 0.51); $I^2 = 0\%$						
Test for overall effect: Z = 1.00 (P = 0.32)						
Test for subgroup differences: Not applicable						



Sub-group analysis – reduction pain score at rest



Study or Subgroup	Paracetamol Mean	SD	Total	Combination Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
4.1.2 Recommended Dose NSAID								
Bondarsky	-17	33.5	30	-21	36	30	1.5%	4.00 [-13.60, 21.60]
Hung	-12	16.5	219	-13	16.5	217	48.9%	1.00 [-2.10, 4.10]
Ridderikhof	-12.3	18.9	167	-11.8	16.2	169	33.1%	-0.50 [-4.27, 3.27]
Subtotal (95% CI)			**416**			**416**	**83.5%**	**0.46 [-1.91, 2.83]**
Heterogeneity: Chi² = 0.52, df = 2 (P = 0.77); I² = 0%								
Test for overall effect: Z = 0.38 (P = 0.70)								
4.1.3 Less Than Recommended Dose NSAID								
Man	-9.4	7.5	16	-9.5	7.1	11	15.1%	0.10 [-5.48, 5.68]
Woo	-12.9	48	64	-16.1	70	92	1.4%	3.20 [-15.32, 21.72]
Subtotal (95% CI)			**80**			**103**	**16.5%**	**0.36 [-4.98, 5.70]**
Heterogeneity: Chi² = 0.10, df = 1 (P = 0.75); I² = 0%								
Test for overall effect: Z = 0.13 (P = 0.90)								
Total (95% CI)			**496**			**519**	**100.0%**	**0.44 [-1.72, 2.61]**
Heterogeneity: Chi² = 0.62, df = 4 (P = 0.96); I² = 0%								
Test for overall effect: Z = 0.40 (P = 0.69)								
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.97), I² = 0%								