SUPPLEMENTARY APPENDIX 7: Network Meta-Analyses (NMA) to Support Decision-Making Regarding Use of Anti-Inflammatory Agents

2020 American College of Rheumatology Guideline for the Management of Gout

PICO 32. For patients experiencing a gout flare, what is the relative impact of colchicine, NSAIDs, systematic glucocorticoids, intra-articular glucocorticoids, ACTH or IL-1 inhibition?

Summary

We found 30 studies (reported by 31 articles) addressing this question (Alloway 1993, Altman 1988, Axelrod 1988, Butler 1985, Cheng 2004, Douglas 1966, Eberl 1985, Fraser 1987, Janssens 2008, Janssen 2018, Lederman 1990, Li 2013, Maccagno 2008, Man 2006, Navarra 2007, Rainer 2016, Rubin 2004, Roddy 2019, Schlesinger 2011, Schlesinger 2012(β-RELIEVED), Schlesinger 2012(β-RELIEVED-II), Schumacher 2002, Schumacher 2012, Siegel 1994, Smyth 1973, Terkeltaub 2013, Willburger 2007, Xu 2015, Xu 2016, Zhang 2014).

To be able to conduct the network meta-analysis, we had to group some of the treatments together in what we describe as "intervention nodes" (Table 1a). For example, the node "Profens" includes ketoprofen, naproxen, flurbiprofen. The core team guided this classification. We provide results according to intervention node. Please refer to Table 1a for categorization of drugs summarized below. Note that some agents could not be analyzed in the NMA because their outcomes were reported differently, precluding their ability to be pooled, or the comparisons between interventions were not connected to the network by any reference.

The evidence shows:

- Canakinumab is probably the most effective for reducing pain at day 2. Intravenous or intramuscular corticosteroids are less effective compared with canakinumab but may be more effective than the other drugs. Rilonacept is likely more effective than the reference (acetic acid derivatives) but inferior to intravenous or intramuscular corticosteroids and canakinumab. All the other drugs might not have different efficacy in terms of pain reduction at day 2.
- Canakinumab is the only intervention that may be better than the reference (acetic acid derivatives) for reducing pain at the longest follow-up. All the other drugs might not have different efficacy.
- Canakinumab may be the only intervention that is better than the reference (acetic acid derivatives) for improving joint tenderness at day 2. All the other drugs may not have different efficacy.
- There may be no differences among the drugs for improving joint tenderness at the longest follow-up.
- Canakinumab is probably the most effective intervention for improving joint

swelling at day 2. Profens the only interventions that are worse than the reference (acetic acid derivatives). There may be no difference among the other drugs for improving joint swelling at day 2.

- There may be no difference among the drugs for improving joint swelling at the longest follow-up.
- There may be no difference among the drugs for patient global assessment at day 2.
- Acetic acid derivatives is probably more effective than profens regarding patient global assessment at longest follow-up.
- Oral corticosteroids are the only interventions that may cause less serious adverse events than acetic acid derivatives.
- Anakinra is non-inferior to a free choice of a free choice of colchicine, naproxen, or prednisolone in terms of pain reduction, patient global assessment, joint tenderness, joint swelling at longest follow-up.

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Table 1a: Drugs included in each intervention node

Category of pharmacological mechanism	Intervention node	Pharmacological interventions included in each node
Corticosteroids	corticosteroids-po	prednisolone
	corticosteroids-im or iv	compound betamethasone, methylprednisolone, triamcinolone acetonide
Colchicine	colchicine	colchicine
ACTH	ACTH	ACTH
NSAIDs	acetic acid derivatives NSAIDs	etodolac, indomethacin, diclofenac
	profens NSAIDs	ketoprofen, naproxen, flurbiprofen
	pyrazolidine derivatives NSAIDs	phenylbutazone, azapropazone
	fenamates NSAIDs	meclofenamate sodium, flufenamic acid
Selective NSAIDs	COX-2 selective NSAIDs	meloxicam
	COX-2 highly selective NSAIDs	etoricoxib, celecoxib, rofecoxib, lumiracoxib
IL-inhibitors	rilonacept	rilonacept
	canakinumab	canakinumab
	anakinra	anakinra
Acetaminophen	acetaminophen	acetaminophen
Combinations	IL-1 inhibitor + acetic acid derivative NSAIDs	rilonacept+ indomethacin

Table 1b: Most and least efficacious treatment for all the outcomes.

For each outcome, interventions were grouped according to efficacy. Interventions depicted with the same color belong to the same group. Green represents the most effective or safe interventions, red represents the least effective or safe interventions, yellow and orange represents intermediate efficacy or safety. Anakinra, a free choice of colchicine, naproxen, or prednisolone are not included in this table because they were only compared to one of the others and could not be incorporated in the NMAs. "Green" designates 'good' patient outcomes, while "red" designates 'inferior' patient outcomes (including for the SAEs).

Intervention	Effectiveness outcome								Safety outcome
	Pain score-mean change		Joint tenderness-mean reduction		Joint swelling-mean reduction		Patient global assessment-mean change		Serious adverse event
	Day 2	Longest follow-up	Day 2	Longest follow-up	Day 2	Longest follow-up	Day 2	Longest follow-up	Longest follow-up
Acetic acid derivatives NSAIDs (Reference)									
Canakinumab							-	-	
Corticosteroids-im or iv							-	-	
COX-2 highly selective NSAIDs									
Corticosteroids-po							-	-	
Profens NSAIDs									
Rilonacept			-	-	-	-	-	-	
IL-1 inhibition + acetic acid derivatives NSAIDs			-	-	-	-	-	-	
Colchicine			-	-	-	-	-	-	
Pyrazolidine derivatives NSAIDs	-	-	-	-	-	-	-	-	
ACTH	-	-	-	-	-	-	-	-	
COX-2 selective NSAIDs	-	-	-	-	-	-	-	-	
Fenamates NSAIDs	-	-	-	-	-	-	-	-	
Cell color pattern‡‡									-
Category	Most effectivenes/safety high/moderate quality	Most effectivenes/safety low/very low quality			Least effectiveness/safety high/moderate quality	Least effectivenes/safety low/very low quality			No study for that outcome

Figure 1: Network plot for pain-mean reduction on Day 2

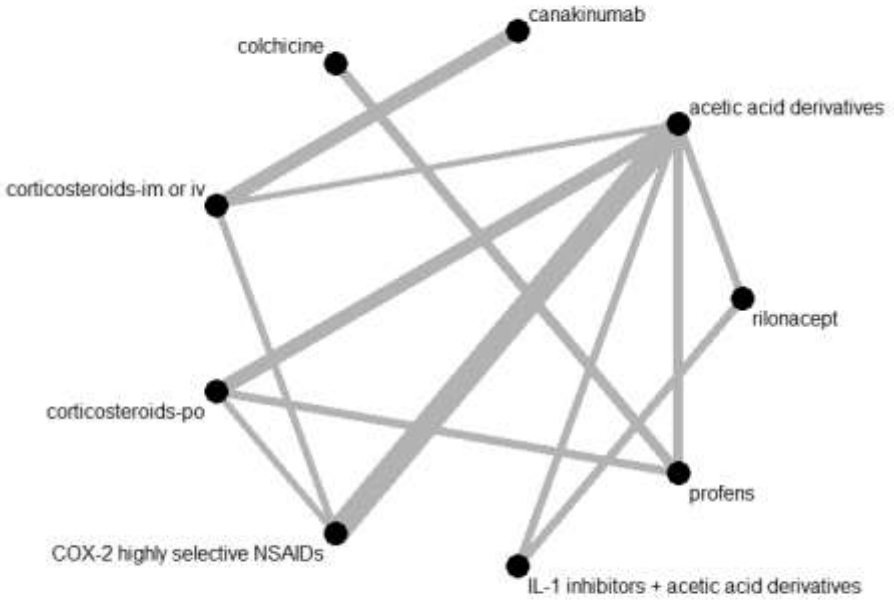


Table 2: Comparisons, estimates and certainty for pain- expressed as the standardized mean difference in pain reduction on Day 2
(measured using different scales, analyzed using the standardized mean difference.)
Estimates presented correspond to Treatment 1 (intervention) compared with Treatment 2 (comparison). Positive numbers indicate a larger reduction of pain levels with Treatment 2 (favors Treatment 2); while negative numbers indicate a larger reduction of pain levels with Treatment 1 (favors treatment 1). Standardized mean differences (SMD)= 0.2 or -0.2 indicate small effects; SMD – 0.5 or -0.5 indicate medium effects; and SMD= 0.8 or -0.8 indicate large effects.

Treatment 1 vs. Treatment 2	**Direct estimates; Certainty of evidence**	**Indirect estimate; Certainty of evidence**	**NMA estimates; Certainty of evidence**	**Reason**
acetic acid derivatives vs. canakinumab	-	1.78 (1.26, 2.31); moderate	1.78 (1.26, 2.31); moderate	RoB
acetic acid derivatives vs. colchicine	-	-0.47 (-1.04, 0.11); low	-0.46 (-1.04, 0.11); low	RoB; imprecision
acetic acid derivatives vs. corticosteroids-im or iv	0.7 (0.18, 1.22); moderate	1.86 (1.27, 2.45); moderate	1.33 (0.9, 1.77); low	RoB; incoherence
acetic acid derivatives vs. corticosteroids-po	-0.12 (-0.53, 0.29); very low	-0.39 (-0.98, 0.2); very low	-0.2 (-0.46, 0.06); very low	RoB; imprecision
acetic acid derivatives vs. COX-2 highly selective NSAIDs	-0.03 (-0.17, 0.11); low	-0.79 (-1.48, -0.1); very low	-0.08 (-0.26, 0.1); low	RoB; imprecision
acetic acid derivatives vs. IL-1 inhibitors + acetic acid derivatives	0.26 (-0.07, 0.58); low	-	0.28 (-0.23, 0.78); low	RoB; imprecision
acetic acid derivatives vs. profens	-0.38 (-0.74, -0.01); moderate	-0.09 (-0.7, 0.51); very low	-0.27 (-0.64, 0.09); low	RoB; imprecision

acetic acid derivatives vs. rilonacept	0.51 (0.19, 0.84); moderate	-	0.51 (0, 1.02); moderate	RoB
canakinumab vs. colchicine	-	-2.25 (-3.03, -1.47); low	-2.25 (-3.03, -1.47); low	RoB; intransitivity
canakinumab vs. corticosteroids-im or iv	-0.44 (-0.61, -0.27); high	-	-0.45 (-0.74, -0.16); high	-
canakinumab vs. corticosteroids-po	-	-1.98 (-2.56, -1.39); very low	-1.98 (-2.56, -1.39); very low	RoB; intransitivity
canakinumab vs. COX-2 highly selective NSAIDs	-	-1.86 (-2.39, -1.34); low	-1.86 (-2.39, -1.34); low	RoB; intransitivity
canakinumab vs. IL-1 inhibitors + acetic acid derivatives	-	-1.51 (-2.24, -0.78); low	-1.51 (-2.24, -0.78); low	RoB; intransitivity
canakinumab vs. profens	-	-2.06 (-2.7, -1.42); low	-2.06 (-2.7, -1.42); low	RoB; intransitivity
canakinumab vs. rilonacept	-	-1.28 (-2.01, -0.55); low	-1.28 (-2.01, -0.55); low	RoB; intransitivity
colchicine vs. corticosteroids-im or iv	-	1.8 (1.08, 2.52); moderate	1.8 (1.08, 2.52); moderate	RoB
colchicine vs. cortcosteroids-po	-	0.27 (-0.31, 0.86); low	0.27 (-0.31, 0.86); low	RoB; imprecision
colchicine vs. COX-2 highly selective NSAIDs	-	0.39 (-0.21, 0.99); low	0.39 (-0.21, 0.99); low	RoB; imprecision
colchicine vs. IL-1 inhibitors + acetic acid derivatives	-	0.74 (-0.02, 1.51); low	0.74 (-0.02, 1.51); low	RoB; imprecision
colchicine vs. profens	0.19 (-0.03, 0.41); low	-	0.19 (-0.25, 0.64); low	RoB; imprecision
colchicine vs. rilonacept	-	0.97 (0.21, 1.74); moderate	0.97 (0.21, 1.74); moderate	RoB

corticosteroids-im or iv vs. corticosteroids-po	-	-1.53 (-2.03, -1.02); low	-1.53 (-2.03, -1.02); low	RoB; inconsistency
corticosteroids-im or iv vs. COX-2 highly selective NSAIDs	-1.89 (-2.3, -1.48); moderate	-0.73 (-1.4, -0.05); moderate	-1.41 (-1.85, -0.98); low	RoB; incoherence
corticosteroids-im or iv vs. IL-1 inhibitors + acetic acid derivatives	-	-1.06 (-1.73, -0.39); moderate	-1.06 (-1.73, -0.39); moderate	RoB
corticosteroids-im or iv vs. profens	-	-1.61 (-2.17, -1.04); moderate	-1.61 (-2.17, -1.04); moderate	RoB
corticosteroids-im or iv vs. rilonacept	-	-0.83 (-1.5, -0.16); moderate	-0.83 (-1.5, -0.16); moderate	RoB
corticosteroids-po vs. COX-2 highly selective NSAIDs	0.14 (-0.31, 0.6); low	0.1 (-0.26, 0.46); very low	0.11 (-0.2, 0.42); very low	RoB; inconsistency; imprecison
corticosteroids-po vs. IL-1 inhibitors + acetic acid derivatives	-	0.47 (-0.1, 1.04); very low	0.47 (-0.1, 1.04); very low	RoB; inconsistency; imprecison
corticosteroids-po vs. profens	0.06 (-0.3, 0.41); moderate	-0.23 (-0.77, 0.31); very low	-0.08 (-0.46, 0.29); very low	RoB; inconsistency; incoherence; imprecison
corticosteroids-po vs. rilonacept	-	0.7 (0.12, 1.27); low	0.7 (0.12, 1.27); low	RoB; inconsistency
COX-2 highly selective NSAIDs vs. IL-1 inhibitors + acetic acid derivatives	-	0.36 (-0.18, 0.89); low	0.36 (-0.18, 0.89); low	RoB; imprecison
COX-2 highly selective NSAIDs vs. profens	-	-0.2 (-0.59, 0.2); low	-0.2 (-0.59, 0.2); low	RoB; imprecison

COX-2 highly selective NSAIDs vs. rilonacept	-	0.59 (0.05, 1.12); moderate	0.59 (0.05, 1.12); moderate	RoB
IL-1 inhibitors + acetic acid derivatives vs. profens	-	-0.55 (-1.17, 0.07); low	-0.55 (-1.17, 0.07); low	RoB; imprecison
IL-1 inhibitors + acetic acid derivatives vs. rilonacept	0.26 (-0.07, 0.58); low	-	0.23 (-0.28, 0.74); low	RoB; imprecison
profens vs. rilonacept	-	0.78 (0.16, 1.41); moderate	0.78 (0.16, 1.41); moderate	RoB

Figure 2: Network plot for pain-mean reduction at longest follow-up

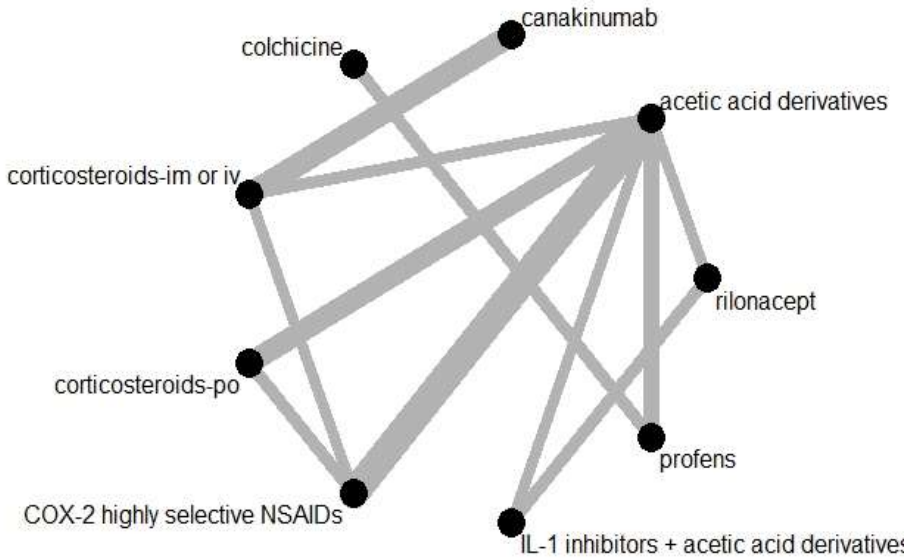


Table 3: Comparisons, estimates and certainty for pain- expressed as the standardized mean difference in pain reduction at longest follow-up (measured using different scales, analyzed using the standardized mean difference.)

Estimates presented correspond to Treatment 1 (intervention) compared with Treatment 2 (comparison). Positive numbers indicate a larger reduction of pain levels with Treatment 2 (favors Treatment 2); while negative numbers indicate a larger reduction of pain levels with Treatment 1 (favors treatment 1). Standardized mean differences (SMD)= 0.2 or -0.2 indicate small effects; SMD – 0.5 or -0.5 indicate medium effects; and SMD= 0.8 or -0.8 indicate large effects.

Treatment 1 vs. Treatment 2	**Direct estimates; Certainty of evidence**	**Indirect estimate; Certainty of evidence**	**NMA estimates; Certainty of evidence**	**Reason**
acetic acid derivatives vs. canakinumab	-	0.81 (0.31, 1.31); moderate	0.81 (0.31, 1.31); moderate	RoB
acetic acid derivatives vs. colchicine	-	-0.31 (-0.97, 0.34); low	-0.31 (-0.97, 0.34); low	RoB; imprecision
acetic acid derivatives vs. corticosteroids-im or iv	-0.07 (-0.58, 0.44); low	0.7 (0.14, 1.25); low	0.36 (-0.05, 0.78); low	RoB; imprecision
acetic acid derivatives vs. corticosteroids-po	0.1 (-0.46, 0.67); very low	-0.17 (-1.29, 0.95); low	0.02 (-0.26, 0.31); very low	RoB; inconsistency; imprecision
acetic acid derivatives vs. COX-2 highly selective NSAIDs	0.02 (-0.12, 0.16); low	-0.47 (-1.13, 0.2); very low	-0.02 (-0.23, 0.19); very low	RoB; incoherence; imprecision
acetic acid derivatives vs. IL-1 inhibitors + acetic acid derivatives	0.1 (-0.22, 0.42); low	-	0.1 (-0.39, 0.59); low	RoB; imprecision
acetic acid derivatives vs. profens	-0.24 (-0.65, 0.18); low	-	-0.24 (-0.74, 0.26); low	RoB; imprecision
acetic acid derivatives vs. rilonacept	0.19 (-0.13, 0.52); low	-	0.2 (-0.29, 0.69); low	RoB; imprecision

canakinumab vs. colchicine	-	-1.12 (-1.95, -0.3); low	-1.12 (-1.95, -0.3); low	RoB; intransitivity
canakinumab vs. corticosteroids-im or iv	-0.46 (-0.64, -0.29); high	-	-0.45 (-0.73, -0.17); moderate	imprecision
canakinumab vs. corticosteroids-po	-	-0.79 (-1.36, -0.22); very low	-0.79 (-1.36, -0.22); very low	RoB; inconsistency; intransitivity
canakinumab vs. COX-2 highly selective NSAIDs	-	-0.83 (-1.32, -0.34); low	-0.83 (-1.32, -0.34); low	RoB; intransitivity
canakinumab vs. IL-1 inhibitors + acetic acid derivatives	-	-0.71 (-1.41, -0.01); low	-0.71 (-1.41, -0.01); low	RoB; intransitivity
canakinumab vs. profens	-	-1.05 (-1.76, -0.34); low	-1.05 (-1.76, -0.34); low	RoB; intransitivity
canakinumab vs. rilonacept	-	-0.61 (-1.31, 0.09); low	-0.61 (-1.31, 0.09); low	RoB; intransitivity
colchicine vs. corticosteroids-im or iv	-	0.67 (-0.1, 1.45); low	0.67 (-0.1, 1.45); low	RoB; imprecision
colchicine vs. corticosteroids-po	-	0.33 (-0.38, 1.05); low	0.33 (-0.38, 1.05); very low	RoB; imprecision
colchicine vs. COX-2 highly selective NSAIDs	-	0.29 (-0.4, 0.98); low	0.29 (-0.4, 0.98); low	RoB; imprecision
colchicine vs. IL-1 inhibitors + acetic acid derivatives	-	0.41 (-0.41, 1.23); low	0.41 (-0.41, 1.23); low	RoB; imprecision
colchicine vs. profens	0.07 (-0.14, 0.28); low	-	0.07 (-0.36, 0.5); low	RoB; imprecision
colchicine vs. rilonacept	-	0.51 (-0.31, 1.33); low	0.51 (-0.31, 1.33); low	RoB; imprecision
corticosteroids-im or iv vs. corticosteroids-po	-	-0.34 (-0.83, 0.16); very low	-0.34 (-0.83, 0.16); very low	RoB; intransitivity; imprecision

corticosteroids-im or iv vs. COX-2 highly selective NSAIDs	-0.67 (-1.01, -0.32); moderate	0.1 (-0.56, 0.76); low	-0.38 (-0.79, 0.02); low	RoB; imprecision
corticosteroids-im or iv vs. IL-1 inhibitors + acetic acid derivatives	-	-0.26 (-0.9, 0.38); low	-0.26 (-0.9, 0.38); low	RoB; imprecision
corticosteroids-im or iv vs. profens	-	-0.6 (-1.25, 0.04); low	-0.6 (-1.25, 0.04); low	RoB; imprecision
corticosteroids-im or iv vs. rilonacept	-	-0.16 (-0.81, 0.48); low	-0.16 (-0.81, 0.48); low	RoB; imprecision
corticosteroids-po vs. COX-2 highly selective NSAIDs	0.04 (-0.42, 0.49); low	-0.08 (-0.48, 0.32); very low	-0.04 (-0.38, 0.29); very low	RoB; imprecision
corticosteroids-po vs. IL-1 inhibitors + acetic acid derivatives	-	0.08 (-0.49, 0.64); very low	0.08 (-0.49, 0.64); very low	RoB; inconsistency; imprecision
corticosteroids-po vs. profens	-	-0.26 (-0.84, 0.31); low	-0.26 (-0.84, 0.31); low	RoB; inconsistency
corticosteroids-po vs. rilonacept	-	0.18 (-0.39, 0.74); very low	0.18 (-0.39, 0.74); low	RoB; inconsistency
COX-2 highly selective NSAIDs vs. IL-1 inhibitors + acetic acid derivatives	-	0.12 (-0.41, 0.65); low	0.12 (-0.41, 0.65); low	RoB; imprecision
COX-2 highly selective NSAIDs vs. profens	-	-0.22 (-0.76, 0.32); low	-0.22 (-0.76, 0.32); low	RoB; imprecision
COX-2 highly selective NSAIDs vs. rilonacept	-	0.22 (-0.31, 0.75); low	0.22 (-0.31, 0.75); low	RoB; imprecision
IL-1 inhibitors + acetic acid derivatives vs. profens	-	-0.34 (-1.04, 0.36); low	-0.34 (-1.04, 0.36); low	RoB; imprecision
IL-1 inhibitors + acetic acid derivatives: vs. rilonacept	0.11 (-0.22, 0.43); low	-	0.1 (-0.39, 0.59); low	RoB; imprecision

profens vs. rilonacept	-	0.44 (-0.26, 1.14); low	0.44 (-0.26, 1.14); low	RoB; imprecision

Figure 3: Network plot for joint tenderness-mean reduction on Day 2

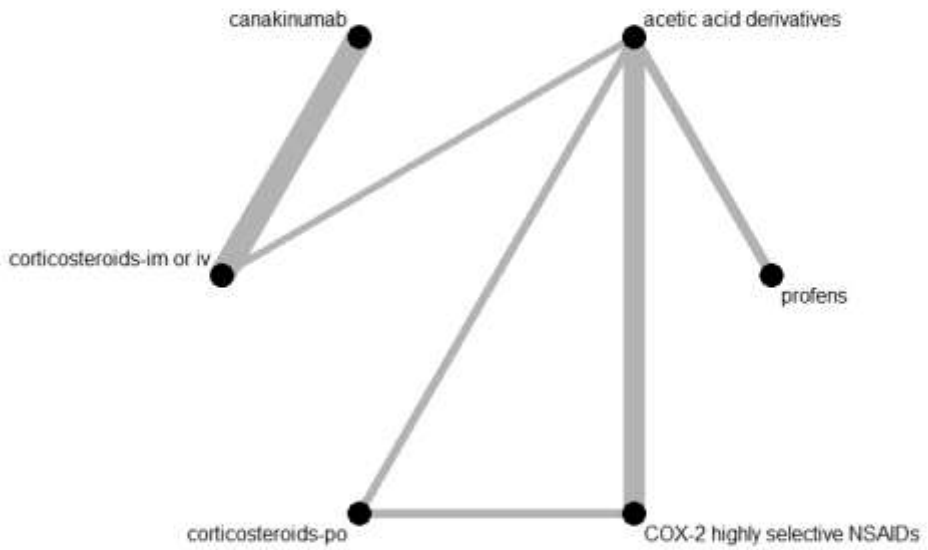


Table 4: Comparisons, estimates and certainty for joint tenderness- expressed as the standardized mean difference in joint tenderness reduction on Day 2 (measured using different scales, analyzed using the standardized mean difference.)

Estimates presented correspond to Treatment 1 (intervention) compared with Treatment 2 (comparison). Positive numbers indicate a larger reduction of joint tenderness with Treatment 2 (favors Treatment 2); while negative numbers indicate a larger reduction of joint tenderness with Treatment 1 (favors treatment 1). Standardized mean differences (SMD)= 0.2 or -0.2 indicate small effects; SMD – 0.5 or -0.5 indicate medium effects; and SMD= 0.8 or -0.8 indicate large effects.

Treatment 1 vs. Treatment 2	**Direct estimates; Certainty of evidence**	**Indirect estimate; Certainty of evidence**	**NMA estimates; Certainty of evidence**	**Reason**
acetic acid derivatives vs. canakinumab	-	0.98 (0.44, 1.52); moderate	0.98 (0.44, 1.52); moderate	intransitivity
acetic acid derivatives vs. corticosteroids-im or iv	0.49 (-0.02, 1.01); low	-	0.49 (-0.02, 1); low	RoB; imprecision
acetic acid derivatives vs. corticosteroids-po	0.24 (-0.23, 0.72); low	0.43 (-0.49, 1.34); low	0.28 (-0.14, 0.7); low	RoB; imprecision
acetic acid derivatives vs. COX-2 highly selective NSAIDs	0.07 (-0.12, 0.26); low	-	0.07 (-0.12, 0.26); low	RoB; imprecision
acetic acid derivatives vs. profens	-0.24 (-0.93, 0.45); low	-	-0.24 (-0.6, 0.12); low	RoB; imprecision
canakinumab vs. corticosteroids-im or iv	-0.49 (-0.66, -0.32); high	-	-0.49 (-0.66, -0.32); high	-
canakinumab vs. corticosteroids-po	-	-0.7 (-1.39, -0.01); low	-0.7 (-1.39, -0.01); low	RoB; intransitivity
canakinumab vs. COX-2 highly selective NSAIDs	-	-0.91 (-1.49, -0.33); low	-0.91 (-1.49, -0.33); low	RoB; intransitivity

canakinumab vs. profens	-	-1.22 (-1.87, -0.57); low	-1.22 (-1.87, -0.57); low	RoB; intransitivity
corticosteroids-im or iv vs. corticosteroids-po	-	-0.21 (-0.87, 0.46); low	-0.21 (-0.87, 0.46); low	RoB; imprecision
corticosteroids-im or iv vs. COX-2 highly selective NSAIDs	-	-0.42 (-0.97, 0.13); low	-0.42 (-0.97, 0.13); low	RoB; imprecision
corticosteroids-im or iv vs. profens	-	-0.34 (-1.07, 0.38); low	-0.73 (-1.36, -0.1); moderate	RoB
corticosteroids-po vs. COX-2 highly selective NSAIDs	-0.24 (-0.7, 0.21); low	-0.03 (-1.09, 1.03); low	-0.21 (-0.63, 0.21); low	RoB; imprecision
corticosteroids-po vs. profens	-	-0.52 (-1.07, 0.03); low	-0.52 (-1.07, 0.03); low	RoB; imprecision
COX-2 highly selective NSAIDs vs. profens	-	-0.31 (-0.72, 0.1); low	-0.31 (-0.72, 0.1); low	RoB; imprecision

Figure 4: Network plot for joint tenderness-mean reduction at longest follow-up

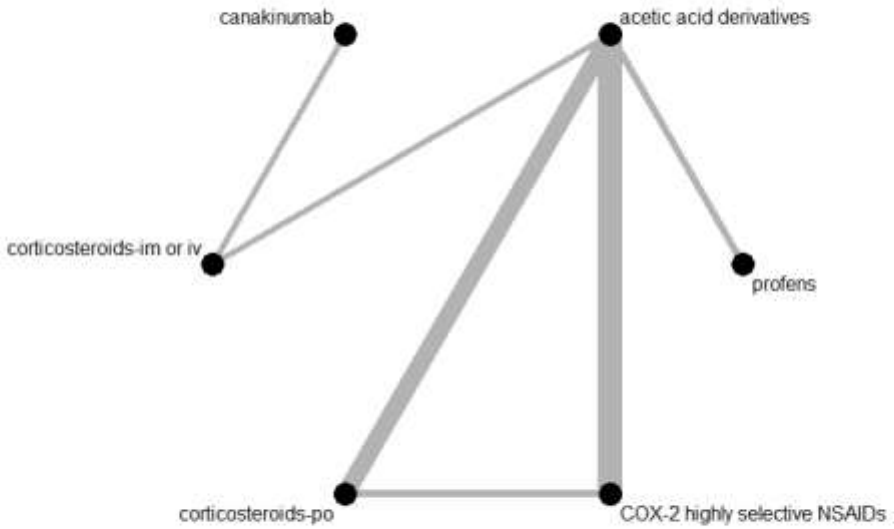


Table 5: Comparisons, estimates and certainty for joint tenderness- expressed as the standardized mean difference in joint tenderness reduction at longest follow-up

(measured using different scales, analyzed using the standardized mean difference.)

Estimates presented correspond to Treatment 1 (intervention) compared with Treatment 2 (comparison). Positive numbers indicate a larger reduction of joint tenderness with Treatment 2 (favors Treatment 2); while negative numbers indicate a larger reduction of joint tenderness with Treatment 1 (favors treatment 1). Standardized mean differences (SMD)= 0.2 or -0.2 indicate small effects; SMD – 0.5 or -0.5 indicate medium effects; and SMD= 0.8 or -0.8 indicate large effects.

Treatment 1 vs. Treatment 2	**Direct estimates; Certainty of evidence**	**Indirect estimate; Certainty of evidence**	**NMA estimates; Certainty of evidence**	**Reason**
acetic acid derivatives vs. canakinumab	-	0.64 (-0.05, 1.33); very low	0.64 (-0.05, 1.33); very low	RoB; imprecision; intransitivity
acetic acid derivatives vs. corticosteroids-im or iv	0 (-0.51, 0.51); low	-	0 (-0.51, 0.51); low	RoB; imprecision
acetic acid derivatives vs. corticosteroids-po	0.01 (-0.17, 0.19); low	0.73 (-0.12, 1.58); low	0.04 (-0.13, 0.22); low	RoB; imprecision
acetic acid derivatives vs. COX-2 highly selective NSAIDs	0.02 (-0.14, 0.17); low	-0.07 (-0.89, 0.75); low	0.02 (-0.12, 0.16); low	RoB; imprecision
acetic acid derivatives vs. profens	-0.29 (-0.71, 0.12); low	-	-0.29 (-0.71, 0.12); low	RoB; imprecision
canakinumab vs. corticosteroids-im or iv	-0.64 (-1.11, -0.17); high	-	-0.64 (-1.11, -0.17); high	-
canakinumab vs. corticosteroids-po	-	-0.6 (-1.31, 0.12); very low	-0.6 (-1.31, 0.12); very low	RoB; imprecision; inconsistency
canakinumab vs. COX-2 highly selective NSAIDs	-	-0.62 (-1.33, 0.08); very low	-0.62 (-1.33, 0.08); very low	RoB; imprecision; inconsistency
canakinumab vs. profens	-	-0.93 (-1.74, -0.13); low	-0.93 (-1.74, -0.13); low	RoB; intransitivity

corticosteroids-im or iv vs. corticosteroids-po	-	0.04 (-0.49, 0.58); low	0.04 (-0.49, 0.58); low	RoB; imprecision
corticosteroids-im or iv vs. COX-2 highly selective NSAIDs	-	0.02 (-0.51, 0.54); low	0.02 (-0.51, 0.54); low	RoB; imprecision
corticosteroids-im or iv vs. profens	-	-0.29 (-0.95, 0.36); low	-0.29 (-0.95, 0.36); low	RoB; imprecision
corticosteroids-po vs. COX-2 highly selective NSAIDs	-0.23 (-0.68, 0.22); low	0.03 (-0.21, 0.28); low	-0.03 (-0.24, 0.19); low	RoB; imprecision
corticosteroids-po vs. profens	-	-0.34 (-0.79, 0.11); low	-0.34 (-0.79, 0.11); low	RoB; imprecision
COX-2 highly selective NSAIDs vs. profens	-	-0.31 (-0.75, 0.13); low	-0.31 (-0.75, 0.13); low	RoB; imprecision

Figure 5: Network plot for joint swelling-mean reduction on Day 2

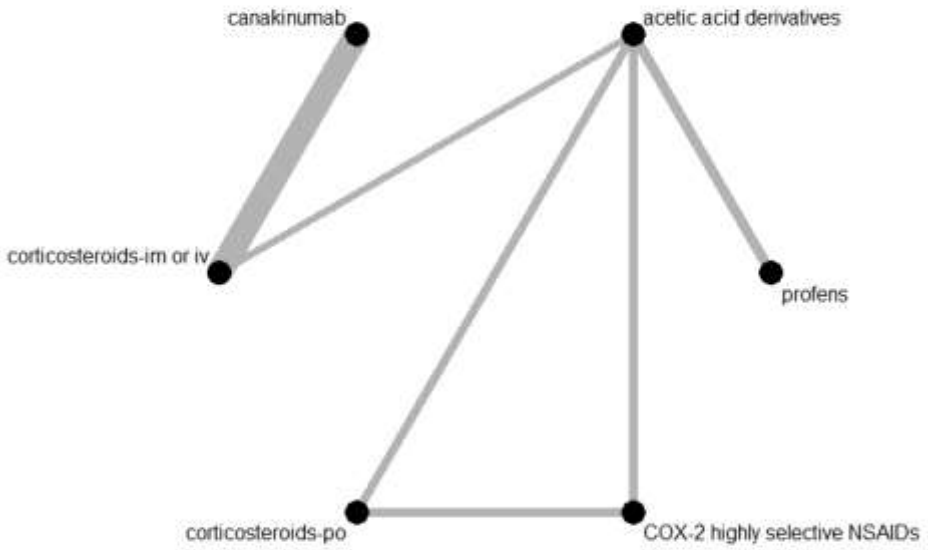


Table 6: Comparisons, estimates and certainty for joint swelling- expressed as the standardized mean difference in joint swelling reduction on Day 2 (measured using different scales, analyzed using the standardized mean difference.)

Estimates presented correspond to Treatment 1 (intervention) compared with Treatment 2 (comparison). Positive numbers indicate a larger reduction of joint tenderness with Treatment 2 (favors Treatment 2); while negative numbers indicate a larger reduction of joint tenderness with Treatment 1 (favors treatment 1). Standardized mean differences (SMD)= 0.2 or -0.2 indicate small effects; SMD – 0.5 or -0.5 indicate medium effects; and SMD= 0.8 or -0.8 indicate large effects.

Treatment 1 vs. Treatment 2	**Direct estimates; Certainty of evidence**	**Indirect estimate; Certainty of evidence**	**NMA estimates; Certainty of evidence**	**Reason**
acetic acid derivatives vs. canakinumab	-	0.83 (0.29, 1.37); low	0.83 (0.29, 1.37); low	RoB; intransitivity
acetic acid derivatives vs. corticosteroids-im or iv	0.4 (-0.11, 0.91); low	-	0.4 (-0.11, 0.91); low	RoB; imprecision
acetic acid derivatives vs. corticosteroids-po	0.13 (-0.34, 0.61); moderate	-	0.13 (-0.34, 0.61); low	RoB; imprecision
acetic acid derivatives vs. COX-2 highly selective NSAIDs	-0.13 (-0.57, 0.31); low	-	-0.13 (-0.58, 0.31); low	RoB; imprecision
acetic acid derivatives vs. profens	-0.39 (-0.75, -0.03); moderate	-	-0.39 (-0.75, -0.03); moderate	RoB
canakinumab vs. corticosteroids-im or iv	-0.43 (-0.62, -0.25); high	-	-0.43 (-0.6, -0.25); high	-
canakinumab vs. corticosteroids-po	-	-0.69 (-1.41, 0.02); very low	-0.69 (-1.41, 0.02); very low	RoB; imprecision; intransitivity
canakinumab vs. COX-2 highly selective NSAIDs	-	-0.96 (-1.66, -0.26); low	-0.96 (-1.66, -0.26); low	RoB; intransitivity

canakinumab vs. profens	-	-1.22 (-1.87, -0.57); low	-1.22 (-1.87, -0.57); low	RoB; intransitivity
corticosteroids-im or iv vs. corticosteroids-po	-	-0.27 (-0.96, 0.43); low	-0.27 (-0.96, 0.43); low	RoB; imprecision
corticosteroids-im or iv vs. COX-2 highly selective NSAIDs	-	-0.54 (-1.21, 0.14); low	-0.54 (-1.21, 0.14); low	RoB; imprecision
corticosteroids-im or iv vs. profens	-	-0.8 (-1.42, -0.17); moderate	-0.8 (-1.42, -0.17); moderate	RoB
corticosteroids-po vs. COX-2 highly selective NSAIDs	-0.27 (-0.72, 0.19); low	-	-0.27 (-0.72, 0.19); low	RoB; imprecision
corticosteroids-po vs. profens	-	-0.53 (-1.12, 0.07); low	-0.53 (-1.12, 0.07); low	RoB; imprecision
COX-2 highly selective NSAIDs vs. profens	-	-0.26 (-0.83, 0.31); low	-0.26 (-0.83, 0.31); low	RoB; imprecision

Figure 6: Network plot for joint swelling-mean reduction at longest follow-up

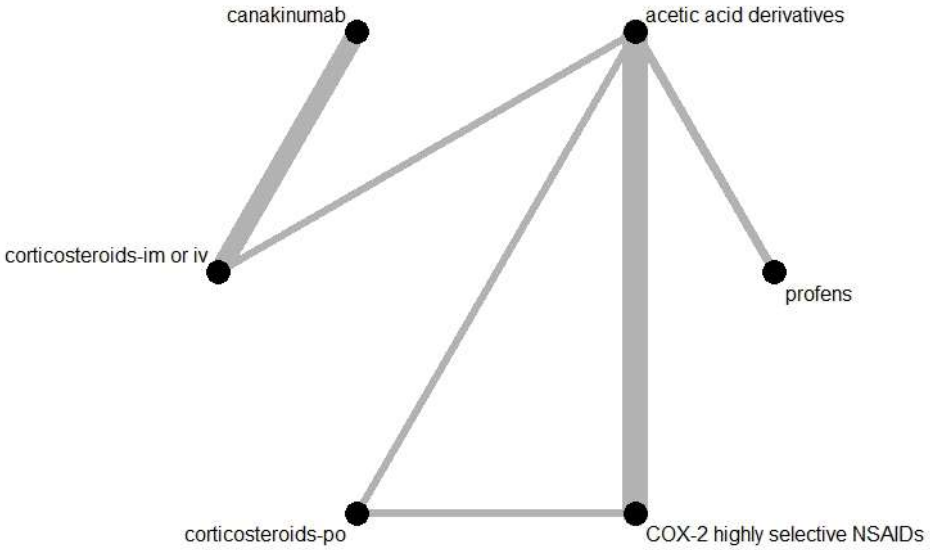


Table 7: Comparisons, estimates and certainty for joint swelling- expressed as the standardized mean difference in joint swelling reduction at longest follow-up

(measured using different scales, analyzed using the standardized mean difference.)

Estimates presented correspond to Treatment 1 (intervention) compared with Treatment 2 (comparison). Positive numbers indicate a larger reduction of joint tenderness with Treatment 2 (favors Treatment 2); while negative numbers indicate a larger reduction of joint tenderness with Treatment 1 (favors treatment 1). Standardized mean differences (SMD)= 0.2 or -0.2 indicate small effects; SMD – 0.5 or -0.5 indicate medium effects; and SMD= 0.8 or -0.8 indicate large effects.

Treatment 1 vs. Treatment 2	**Direct estimates; Certainty of evidence**	**Indirect estimate; Certainty of evidence**	**NMA estimates; Certainty of evidence**	**Reason**
acetic acid derivatives vs. canakinumab	-	0.38 (-0.21, 0.96); very low	0.38 (-0.21, 0.96); very low	RoB; imprecision; intransitivity
acetic acid derivatives vs. corticosteroids-im or iv	0.04 (-0.47, 0.55); low	-	0.04 (-0.5, 0.59); low	RoB; imprecision
acetic acid derivatives vs. corticosteroids-po	0.45 (-0.02, 0.93); low	-0.23 (-1.16, 0.71); low	0.29 (-0.16, 0.75); low	RoB; imprecision
acetic acid derivatives vs. COX-2 highly selective NSAIDs	0.09 (-0.05, 0.23); low	-	0.09 (-0.07, 0.26); low	RoB; imprecision
acetic acid derivatives vs. profens	0.01 (-0.58, 0.6); very low	-	0.05 (-0.39, 0.49); very low	RoB; inconsistency; imprecision
canakinumab vs. corticosteroids-im or iv	-0.36 (-0.66, -0.05); high	-	-0.33 (-0.35, -0.12); high	-
canakinumab vs. corticosteroids-po	-	-0.08 (-0.83, 0.66); very low	-0.08 (-0.83, 0.66); very low	RoB; imprecision; intransitivity
canakinumab vs. COX-2 highly selective NSAIDs	-	-0.28 (-0.89, 0.33); very low	-0.28 (-0.89, 0.33); very low	RoB; imprecision; iintransitivity

canakinumab vs. profens	-	-0.33 (-1.06, 0.41); very low	-0.33 (-1.06, 0.41); very low	RoB; inconsistency; imprecision; intransitivity
corticosteroids-im or iv vs. corticosteroids-po	-	0.25 (-0.46, 0.96); low	0.25 (-0.46, 0.96); low	RoB; imprecision
corticosteroids-im or iv vs. COX-2 highly selective NSAIDs	-	0.05 (-0.52, 0.62); low	0.05 (-0.52, 0.62); low	RoB; imprecision
corticosteroids-im or iv vs. profens	-	0.01 (-0.7, 0.71); very low	0.01 (-0.7, 0.71); very low	RoB; inconsistency; imprecision; intransitivity
corticosteroids-po vs. COX-2 highly selective NSAIDs	-0.07 (-0.52, 0.38); low	-0.83 (-1.92, 0.26); low	-0.2 (-0.65, 0.25); low	RoB; imprecision
corticosteroids-po vs. profens	-	-0.24 (-0.88, 0.39); very low	-0.24 (-0.88, 0.39); very low	RoB; inconsistency; imprecision; intransitivity
COX-2 highly selective NSAIDs vs. profens	-	-0.04 (-0.52, -0.43); low	-0.04 (-0.52, 0.43); very low	RoB; inconsistency; imprecision; intransitivity

Figure 7: Network plot for patient global assessment-mean change on Day 2

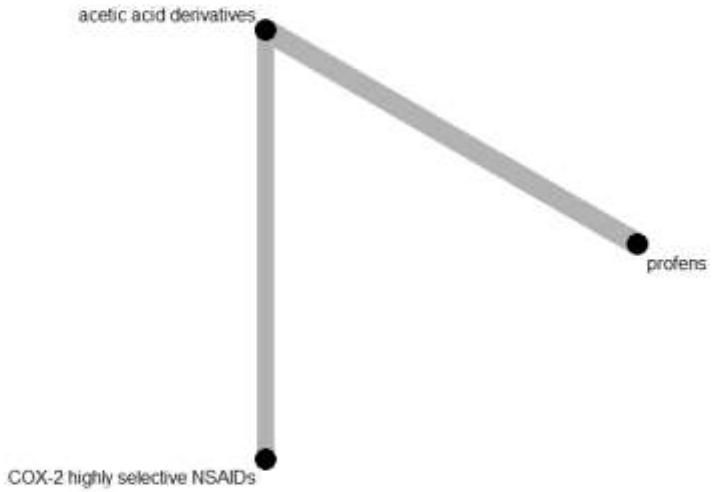


Table 8: Comparisons, estimates and certainty for patient global assessment-expressed as the standardized mean difference in patient global assessment on Day 2

(measured using different scales, analyzed using the standardized mean difference.)

Estimates presented correspond to Treatment 1 (intervention) compared with Treatment 2 (comparison). Positive numbers indicate a larger worsening of patient global assessment with Treatment 1 (favors Treatment 2); while negative numbers indicate a larger worsening of patient global assessment with Treatment 2 (favors treatment 1). Standardized mean differences (SMD)= 0.2 or -0.2 indicate small effects; SMD – 0.5 or -0.5 indicate medium effects; and SMD= 0.8 or -0.8 indicate large effects.

Treatment 1 vs. Treatment 2	**Direct estimates; Certainty of evidence**	**Indirect estimate; Certainty of evidence**	**NMA estimates; Certainty of evidence**	**Reason**
acetic acid derivatives vs. COX-2 highly selective NSAIDs	0.01 (-0.2, 0.23); low	-	0.0101 (-0.98, 1); low	RoB; imprecision
acetic acid derivatives vs. profens	-0.21 (-0.57, 0.15); low	-	-0.21 (-0.98, 0.56); low	RoB; imprecision
COX-2 highly selective NSAIDs vs. profens	-	-0.22 (-1.47, 1.03); low	-0.22 (-1.47, 1.03); low	RoB; imprecision

Figure 8: Network plot for patient global assessment-mean change at longest follow-up

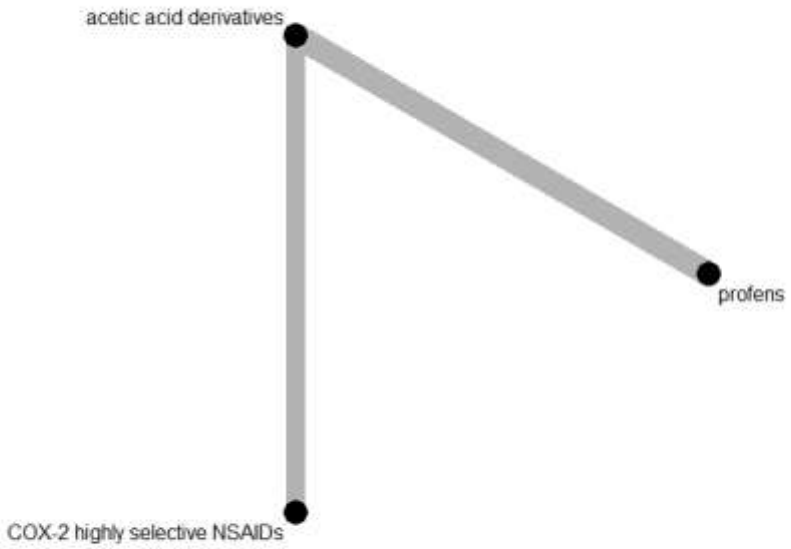


Table 9: Comparisons, estimates and certainty for patient global assessment--expressed as the standardized mean difference in patient global assessment at longest follow-up

(measured using different scales, analyzed using the standardized mean difference.)

Estimates presented correspond to Treatment 1 (intervention) compared with Treatment 2 (comparison). Positive numbers indicate a larger worsening of patient global assessment with Treatment 1 (favors Treatment 2); while negative numbers indicate a larger worsening of patient global assessment with Treatment 2 (favors treatment 1). Standardized mean differences (SMD)= 0.2 or -0.2 indicate small effects; SMD – 0.5 or -0.5 indicate medium effects; and SMD= 0.8 or -0.8 indicate large effects.

Treatment 1 vs. Treatment 2	**Direct estimates; Certainty of evidence**	**Indirect estimate; Certainty of evidence**	**NMA estimates; Certainty of evidence**	**Reason**
acetic acid derivatives vs. COX-2 highly selective NSAIDs	-0.1 (-0.27, 0.08); low	-	-0.0951 (-0.27, 0.08); low	RoB; imprecision
acetic acid derivatives vs. profens	-0.45 (-0.87, -0.03); moderate	-	-0.44 (-0.86, -0.02); moderate	RoB
COX-2 highly selective NSAIDs vs. profens	-	-0.35 (-0.8, 0.11); low	-0.35 (-0.8, 0.11); low	RoB; imprecision

Figure 9: Network plot for serious adverse events

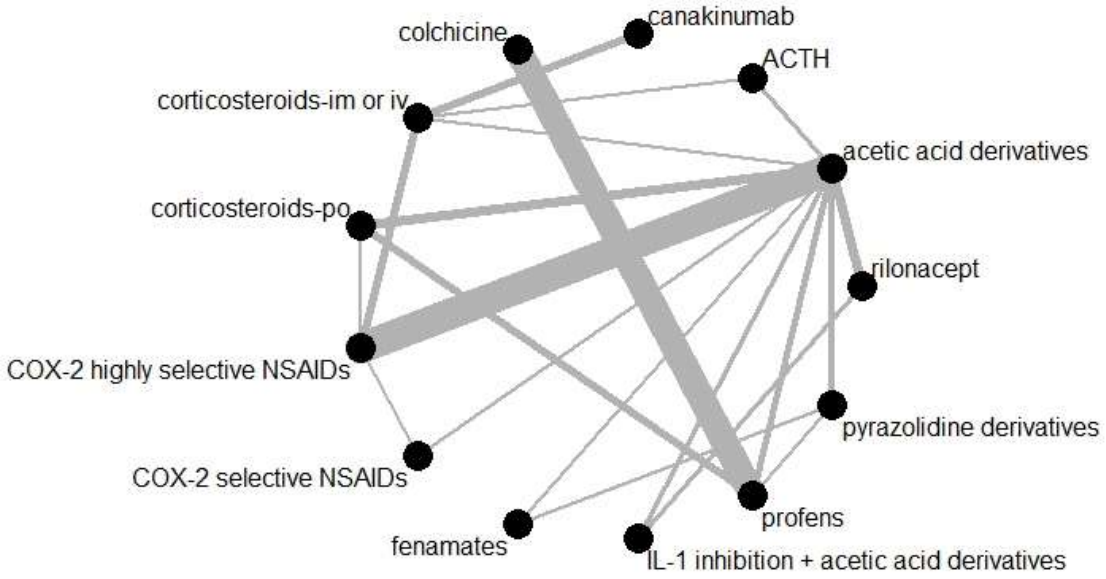


Table 10: Comparisons, estimates and certainty for serious adverse events

(measured as the proportion of people with serious adverse events, analyzed using the risk difference.)

Estimates presented correspond to Treatment 1 (intervention) compared with Treatment 2 (comparison). Positive numbers indicate a larger risk of serious adverse events with Treatment 1 (favors Treatment 2); while negative numbers indicate a larger risk of serious adverse events with Treatment 2 (favors treatment 1).

Treatment 1 vs. Treatment 2	**Direct estimates; Certainty of evidence**	**Indirect estimate; Certainty of evidence**	**NMA estimates; Certainty of evidence**	**Reason**
acetic acid derivatives vs. ACTH	0 (-0.05,0.05); low	0 (-0.12, 0.13); low	0 (-0.05, 0.05); low	RoB; imprecision
acetic acid derivatives vs. canakinumab	-	-0.03 (-0.06, 0.01); low	-0.03 (-0.06, 0.01); low	RoB; imprecision
acetic acid derivatives vs. colchicine	-	0.02 (-0.01, 0.04); low	0.02 (-0.01, 0.04); low	RoB; imprecision
acetic acid derivatives vs. corticosteroids-im or iv	0 (-0.06,0.06); low	0 (-0.03, 0.03); low	0 (-0.02, 0.03); low	RoB; imprecision
acetic acid derivatives vs. corticosteroids-po	0.13 (-0.03,0.29); very low	-0.01 (-0.05, 0.04); low	0.03 (0.01, 0.05); very low	RoB; inconsistency; incoherence; imprecision
acetic acid derivatives vs. COX-2 highly selective NSAIDs	0.01 (-0.01,0.03); low	-0.01 (-0.06, 0.05); very low	0 (0, 0.01); very low	RoB; incoherence; imprecision
acetic acid derivatives vs. COX-2 selective NSAIDs	0 (-0.09,0.09); low	0.01 (-0.15, 0.17); low	0 (-0.08, 0.08); low	RoB; imprecision
acetic acid derivatives vs. fenamates	0 (-0.17,0.17); low	0 (-0.14, 0.15); low	0 (-0.11, 0.11); low	RoB; imprecision
acetic acid derivatives vs. IL-1 inhibition + acetic acid derivatives	-0.04 (-0.09,0.01); low	-	-0.04 (-0.09, 0.01); low	RoB; imprecision

acetic acid derivatives vs. profens	0 (-0.04,0.04); low	0.03 (-0.01, 0.07); very low	0.02 (-0.01, 0.04); very low	RoB; inconsistency; imprecision
acetic acid derivatives vs. pyrazolidine derivatives	0 (-0.04,0.04); low	0.01 (-0.09, 0.11); low	0 (-0.03, 0.04); low	RoB; imprecision
acetic acid derivatives vs. rilonacept	0 (-0.03,0.03); low	-	0 (-0.03, 0.03); low	RoB; imprecision
ACTH vs. canakinumab	-	-0.03 (-0.08, 0.03); low	-0.03 (-0.08, 0.03); low	RoB; imprecision
ACTH vs. colchicine	-	0.02 (-0.04, 0.07); low	0.02 (-0.04, 0.07); low	RoB; imprecision
ACTH vs. corticosteroids-im or iv	0 (-0.12,0.12); low	0 (-0.05, 0.06); low	0 (-0.05, 0.05); low	RoB; imprecision
ACTH vs. corticosteroids-po	-	0.03 (-0.02, 0.08); very low	0.03 (-0.02, 0.08); very low	RoB; inconsistency; imprecision
ACTH vs. COX-2 highly selective NSAIDs	-	0 (-0.04, 0.05); low	0 (-0.04, 0.05); low	RoB; imprecision
ACTH vs. COX-2 selective NSAIDs	-	0 (-0.09, 0.09); low	0 (-0.09, 0.09); low	RoB; imprecision
ACTH vs. fenamates	-	0 (-0.12, 0.12); low	0 (-0.12, 0.12); low	RoB; imprecision
ACTH vs. IL-1 inhibition + acetic acid derivatives	-	-0.04 (-0.11, 0.03); low	-0.04 (-0.11, 0.03); low	RoB; imprecision
ACTH vs. profens	-	0.02 (-0.04, 0.07); low	0.02 (-0.04, 0.07); low	RoB; imprecision
ACTH vs. pyrazolidine derivatives	-	0 (-0.06, 0.06); low	0 (-0.06, 0.06); low	RoB; imprecision
ACTH vs. rilonacept	-	0 (-0.05, 0.05); low	0 (-0.05, 0.05); low	RoB; imprecision
canakinumab vs. colchicine	-	0.04 (-0.01, 0.09); very low	0.04 (-0.01, 0.09); very low	RoB; imprecision
canakinumab vs. corticosteroids-im or iv	0.03 (0,0.06); moderate	-	0.03 (0, 0.06); moderate	imprecision

canakinumab vs. corticosteroids-po	-	0.05 (0.01, 0.1); very low	0.05 (0.01, 0.1); very low	RoB; inconsistency; intransitivity; imprecision
canakinumab vs. COX-2 highly selective NSAIDs	-	0.03 (-0.01, 0.07); very low	0.03 (-0.01, 0.07); very low	RoB; intransitivity; imprecision
anakinumab vs. COX-2 selective NSAIDs	-	0.03 (-0.06, 0.11); very low	0.03 (-0.06, 0.11); very low	RoB; intransitivity; imprecision
canakinumab vs. fenamates	-	0.03 (-0.09, 0.15); very low	0.03 (-0.09, 0.15); very low	RoB; intransitivity; imprecision
canakinumab vs. IL-1 inhibition + acetic acid derivatives	-	-0.02 (-0.08, 0.05); very low	-0.02 (-0.08, 0.05); very low	RoB; intransitivity; imprecision
canakinumab vs. profens	-	0.04 (-0.01, 0.09); very low	0.04 (-0.01, 0.09); very low	RoB; intransitivity; imprecision
canakinumab vs. pyrazolidine derivatives	-	0.03 (-0.03, 0.08); very low	0.03 (-0.03, 0.08); very low	RoB; intransitivity; imprecision
canakinumab vs. rilonacept	-	0.03 (-0.02, 0.07); very low	0.03 (-0.02, 0.07); very low	RoB; intransitivity; imprecision
colchicine vs. corticosteroids-im or iv	-	-0.01 (0.05, 0.03); low	-0.01 (-0.05, 0.03); low	RoB; imprecision
colchicine vs. corticosteroids-po	-	0.01 (-0.01, 0.04); low	0.01 (-0.01, 0.04); low	RoB; imprecision
colchicine vs. COX-2 highly selective NSAIDs	-	-0.01 (-0.04, 0.02); low	-0.01 (-0.04, 0.02); low	RoB; imprecision
colchicine vs. COX-2 selective NSAIDs	-	-0.01 (-0.1, 0.07); low	-0.01 (-0.1, 0.07); low	RoB; imprecision
colchicine vs. fenamates	-	-0.02 (-0.13, 0.1); low	-0.02 (-0.13, 0.1); low	RoB; imprecision

colchicine vs. IL-1 inhibition + acetic acid derivatives	-	-0.06 (-0.11, 0); moderate	-0.06 (-0.11, 0); moderate	RoB
colchicine vs. profens	0 (-0.01,0.01); moderate	-	0 (0, 0); moderate	RoB; imprecision
colchicine vs. pyrazolidine derivatives	-	-0.01 (-0.06, 0.03); low	-0.01 (-0.06, 0.03); low	RoB; imprecision
colchicine vs. rilonacept	-	-0.02 (-0.05, 0.02); low	-0.02 (-0.05, 0.02); low	RoB; imprecision
orticosteroids-im or iv vs. corticosteroids-po	-	0.03 (-0.01, 0.06); very low	0.03 (-0.01, 0.06); very low	RoB; inconsistency; imprecision
corticosteroids-im or iv vs. COX-2 highly selective NSAIDs	0 (-0.03,0.03); low	0 (-0.05, 0.06); low	0 (-0.02, 0.03); low	RoB; imprecision
corticosteroids-im or iv vs. COX-2 selective NSAIDs	-	0 (-0.08, 0.08); low	0 (-0.08, 0.08); low	RoB; imprecision
corticosteroids-im or iv vs. fenamates	-	0 (-0.12, 0.11); low	0 (-0.12, 0.11); low	RoB; imprecision
corticosteroids-im or iv vs. IL-1 inhibition + acetic acid derivatives	-	-0.04 (-0.1, 0.01); low	-0.04 (-0.1, 0.01); low	RoB; imprecision
corticosteroids-im or iv vs. profens	-	0.01 (-0.02, 0.05); low	0.01 (-0.02, 0.05); low	RoB; imprecision
corticosteroids-im or iv vs. pyrazolidine derivatives	-	0 (-0.05, 0.04); low	0 (-0.05, 0.04); low	RoB; imprecision
corticosteroids-im or iv vs. rilonacept	-	0 (-0.04, 0.03); low	0 (-0.04, 0.03); low	RoB; imprecision
corticosteroids-po vs. COX-2 highly selective NSAIDs	-0.01 (-0.12,0.1); low	-0.03 (-0.05, 0); very low	-0.03 (-0.05, 0); very low	RoB; inconsistency; imprecision
corticosteroids-po vs. COX-2 selective NSAIDs	-	-0.03 (-0.11, 0.05); very low	-0.03 (-0.11, 0.05); very low	RoB; inconsistency; imprecision

corticosteroids-po vs. fenamates	-	-0.03 (-0.14, 0.09); very low	-0.03 (-0.14, 0.09); very low	RoB; inconsistency; imprecision
corticosteroids-po vs. IL-1 inhibition + acetic acid derivatives	-	-0.07 (-0.12, -0.01); very low	-0.07 (-0.12, -0.01); very low	RoB; inconsistency; imprecision
corticosteroids-po vs. profens	0 (-0.03,0.03); low	-0.04 (-0.07, 0.01); very low	-0.01 (-0.04, 0.01); very low	RoB; inconsistency; imprecision
corticosteroids-po vs. pyrazolidine derivatives	-	-0.03 (-0.07, 0.01); very low	-0.03 (-0.07, 0.01); very low	RoB; inconsistency; imprecision
corticosteroids-po vs. rilonacept	-	-0.03 (-0.06, 0); very low	-0.03 (-0.06, 0); very low	RoB; inconsistency; imprecision
COX-2 highly selective NSAIDs vs. COX-2 selective NSAIDs	0 (-0.09,0.09); low	-0.01 (-0.15, 0.14); low	0 (-0.08, 0.08); low	RoB; imprecision
COX-2 highly selective NSAIDs vs. fenamates	-	0 (-0.12, 0.11); low	0 (-0.12, 0.11); low	RoB; imprecision
COX-2 highly selective NSAIDs vs. IL-1 inhibition + acetic acid derivatives	-	-0.04 (-0.1, 0.01); low	-0.04 (-0.1, 0.01); low	RoB; imprecision
COX-2 highly selective NSAIDs vs. profens	-	0.01 (-0.02, 0.04); low	0.01 (-0.02, 0.04); low	RoB; imprecision
COX-2 highly selective NSAIDs vs. pyrazolidine derivatives	-	0 (-0.04, 0.04); low	0 (-0.04, 0.04); low	RoB; imprecision
COX-2 highly selective NSAIDs vs. rilonacept	-	0 (-0.03, 0.02); low	0 (-0.03, 0.02); low	RoB; imprecision
COX-2 selective NSAIDs vs. fenamates	-	0 (-0.14, 0.14); low	0 (-0.14, 0.14); low	RoB; imprecision
COX-2 selective NSAIDs vs. IL-1 inhibition + acetic acid derivatives	-	-0.04 (-0.13, 0.05); low	-0.04 (-0.13, 0.05); low	RoB; imprecision

COX-2 selective NSAIDs vs. profens	-	0.01 (-0.07, 0.1); low	0.01 (-0.07, 0.1); low	RoB; imprecision
COX-2 selective NSAIDs vs. pyrazolidine derivatives	-	0 (-0.09, 0.09); low	0 (-0.09, 0.09); low	RoB; imprecision
COX-2 selective NSAIDs vs. rilonacept	-	0 (-0.08, 0.08); low	0 (-0.08, 0.08); low	RoB; imprecision
fenamates vs. IL-1 inhibition + acetic acid derivatives	-	-0.04 (-0.17, 0.08); low	-0.04 (-0.17, 0.08); low	RoB; imprecision
fenamates vs. profens	-	0.01 (-0.1, 0.13); low	0.01 (-0.1, 0.13); low	RoB; imprecision
fenamates vs. pyrazolidine derivatives	0 (-0.15,0.15); moderate	0 (-0.18, 0.18); low	0 (-0.11, 0.11); low	RoB; imprecision
fenamates vs. rilonacept	-	0 (-0.12, 0.12); low	0 (-0.12, 0.12); low	RoB; imprecision
IL-1 inhibition + acetic acid derivatives vs. profens	-	0.06 (0, 0.11); low	0.06 (0, 0.11); low	RoB; imprecision
IL-1 inhibition + acetic acid derivatives vs. pyrazolidine derivatives	-	0.04 (-0.02, 0.1); low	0.04 (-0.02, 0.1); low	RoB; imprecision
IL-1 inhibition + acetic acid derivatives vs. rilonacept	0.04 (-0.01,0.09); low	-	0.04 (-0.01, 0.09); low	RoB; imprecision
profen vs. pyrazolidine derivatives	0 (-0.11,0.11); low	-0.02 (-0.06, 0.03); low	-0.01 (-0.06, 0.03); low	RoB; imprecision
profen vs. rilonacept	-	-0.02 (-0.05, 0.02); low	-0.02 (-0.05, 0.02); low	RoB; imprecision
pyrazolidine derivatives vs. rilonacept	-	0 (-0.05, 0.04); low	0 (-0.05, 0.04); low	RoB; imprecision

Figure 10: Risk of bias assessment

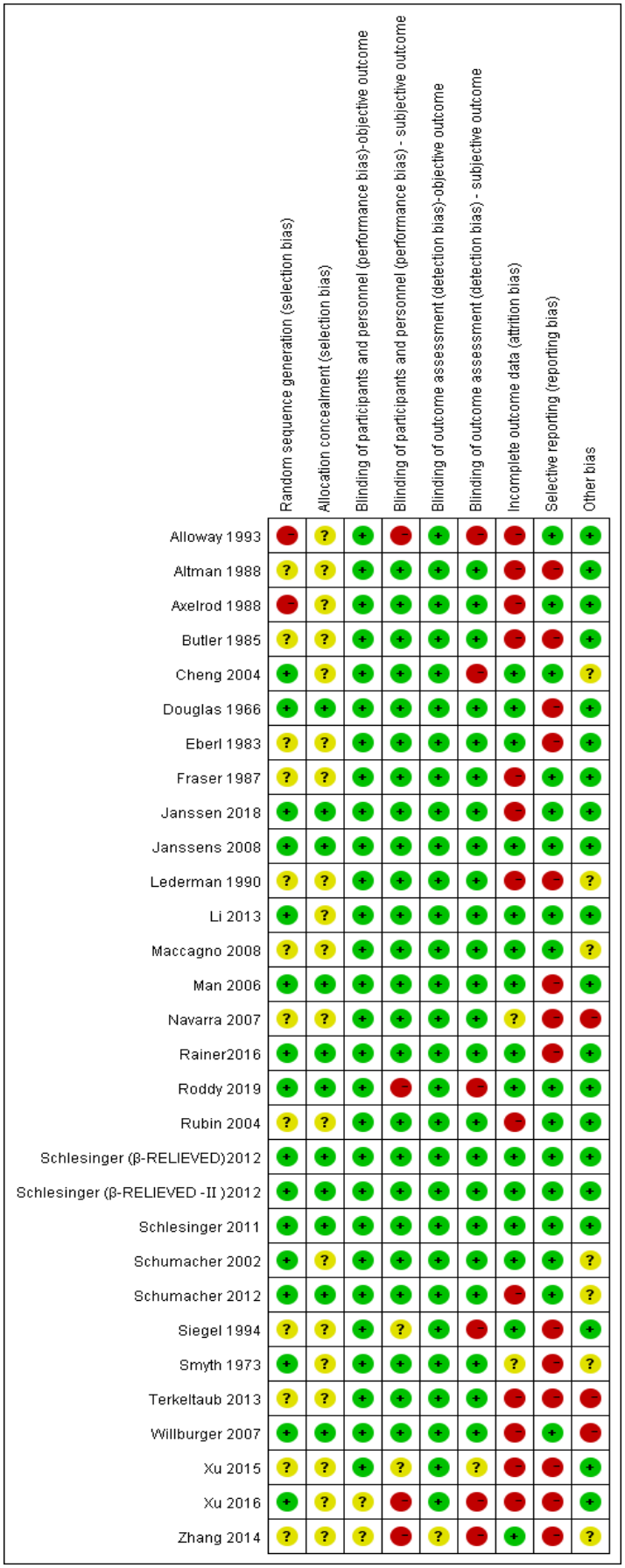
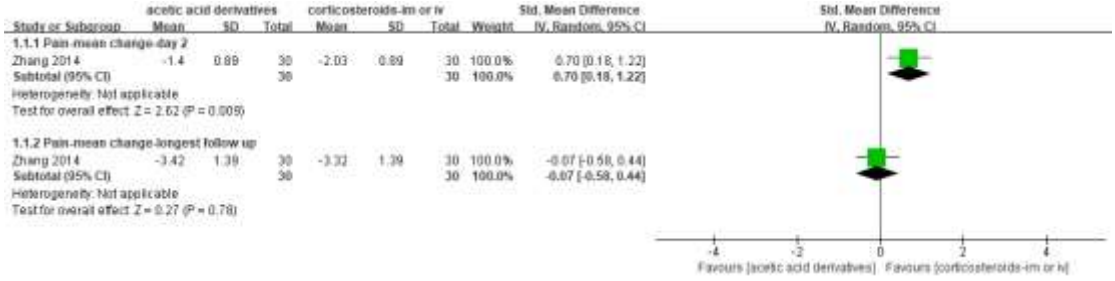


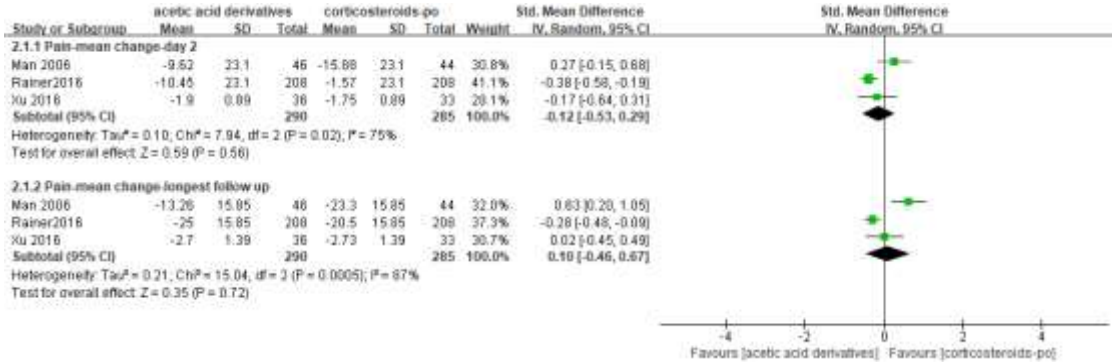
Figure 11: Forest plot of direct comparisons

Outcome: pain-mean change on Day 2 and at longest follow-up

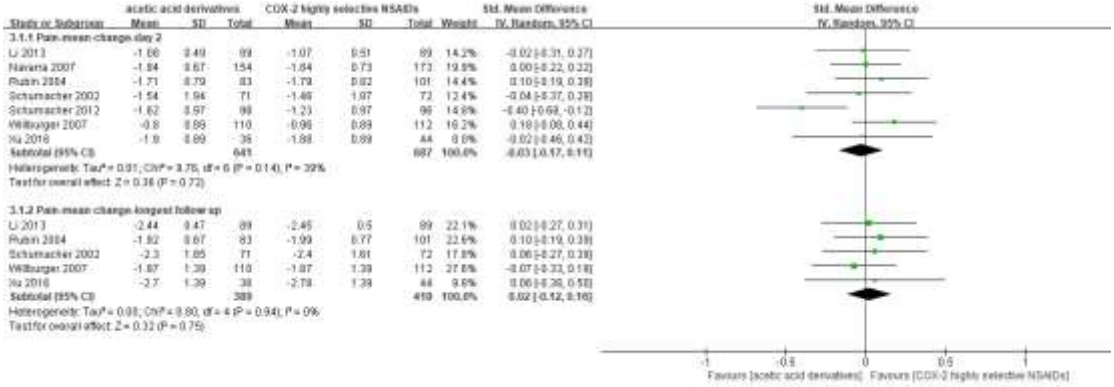
Comparison acetic acid derivatives vs. corticosteroids-im. or iv.



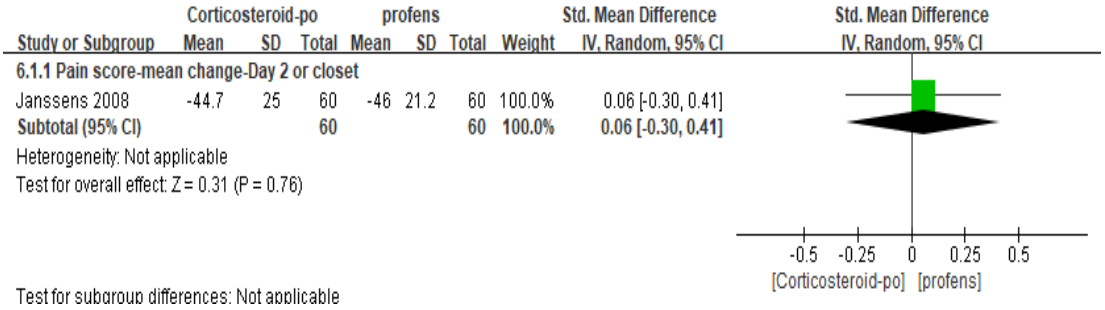
Comparison acetic acid derivatives vs. corticosteroid-po



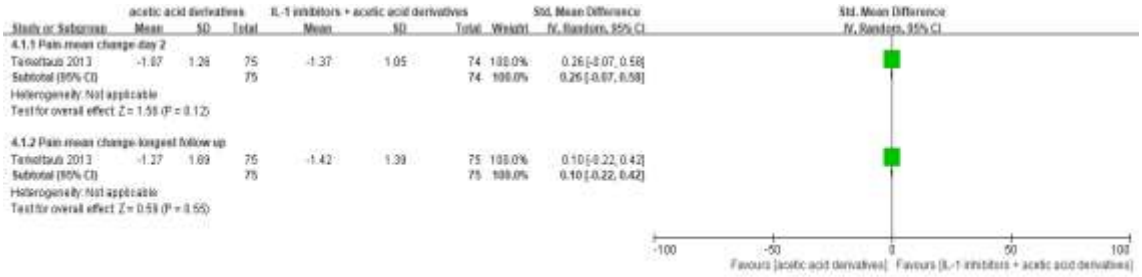
Comparison acetic acid derivatives vs. COX-2 highly selective NSAIDs



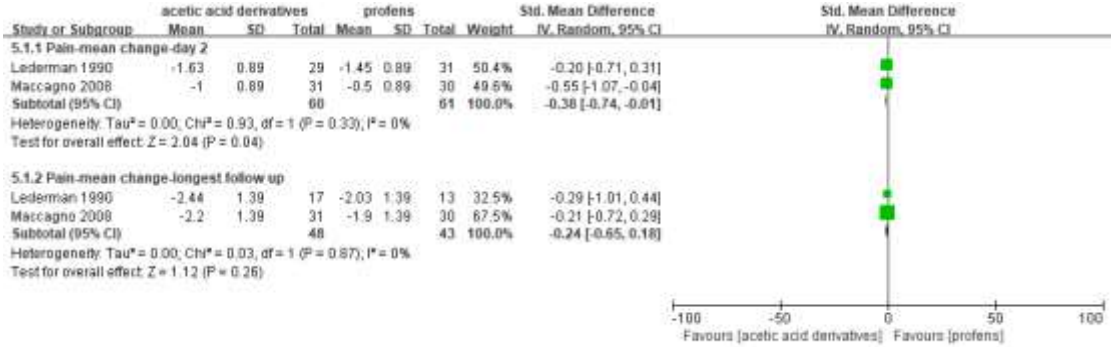
Comparison corticosteroid-po vs. profens



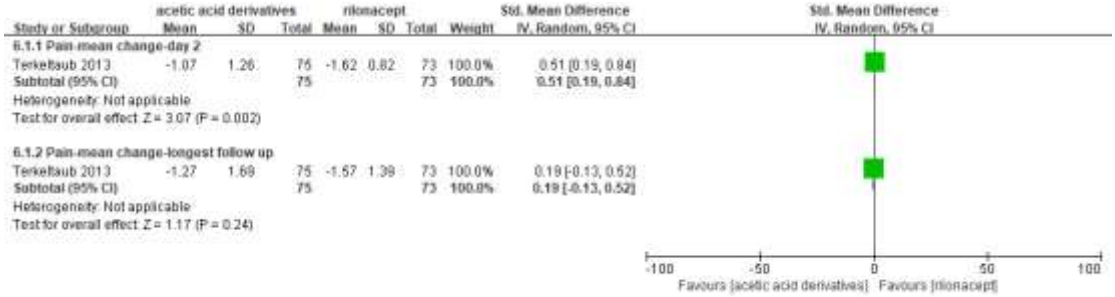
Comparison acetic acid derivatives vs. IL-1 inhibitors + acetic acid derivatives



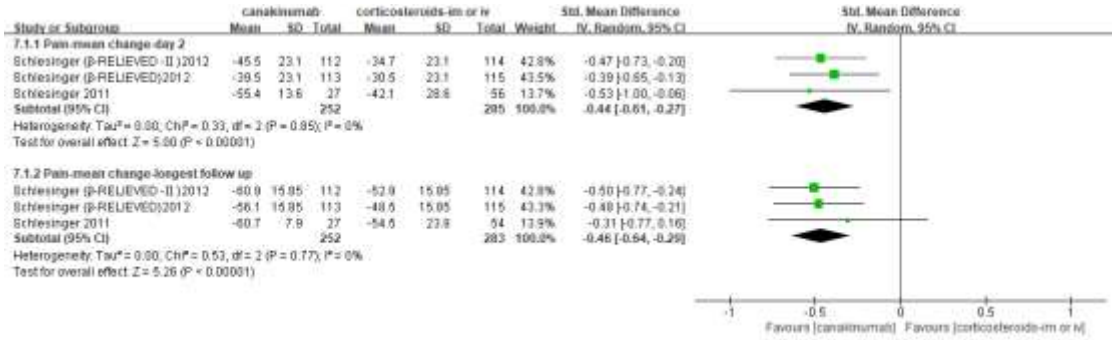
Comparison acetic acid derivatives vs. profens



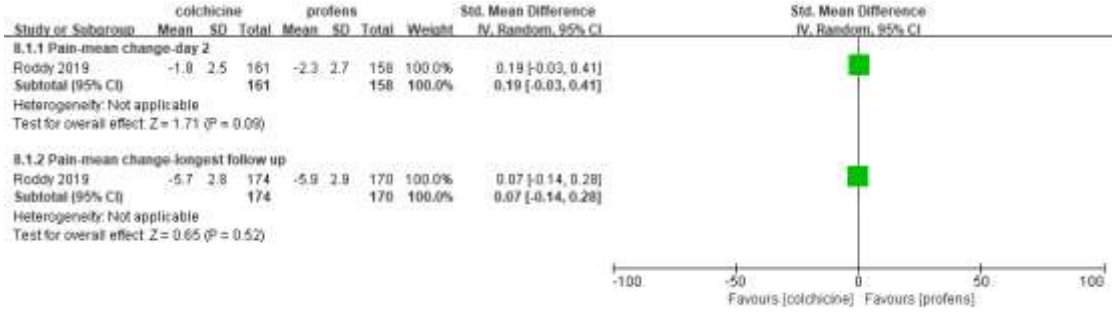
Comparison acetic acid derivatives vs. rilonacept



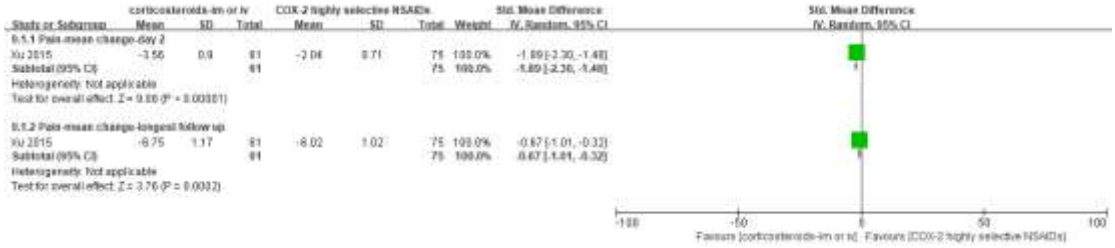
Comparison canakinumab vs. corticosteroids-im or iv



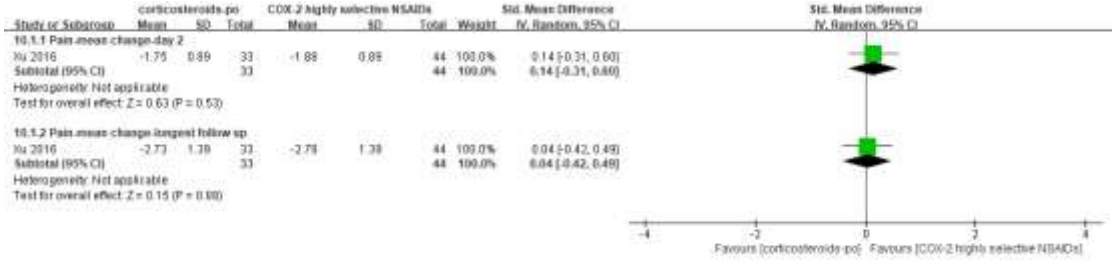
Comparison colchicine vs. profens



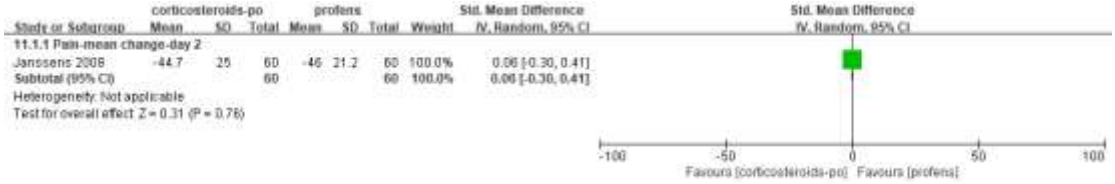
Comparison corticosteroids-im or iv vs. COX-2 highly selective NSAIDs



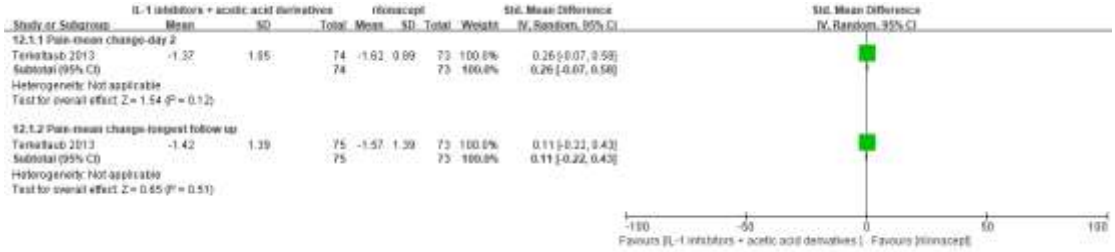
Comparison corticosteroids-po vs. COX-2 highly selective NSAIDs



Comparison corticosteroids-po vs. profens

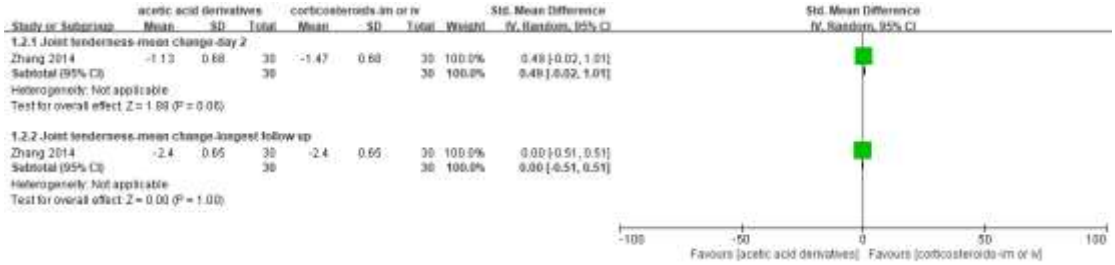


Comparison IL-1 inhibitors + acetic acid derivatives vs. rilonacept

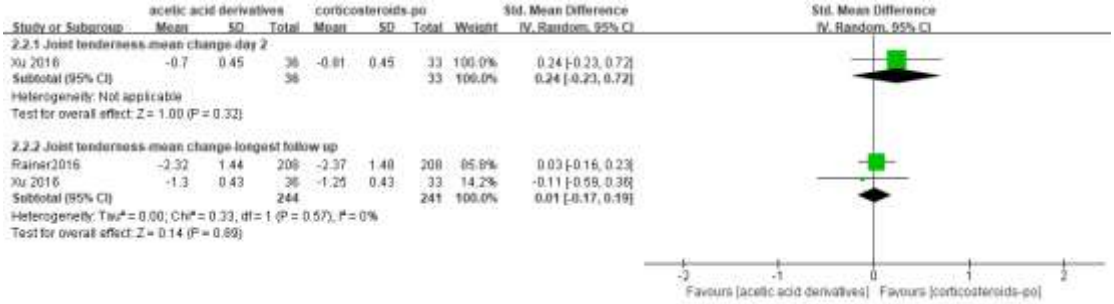


Outcome: joint tenderness-mean change on Day 2 and at longest follow-up

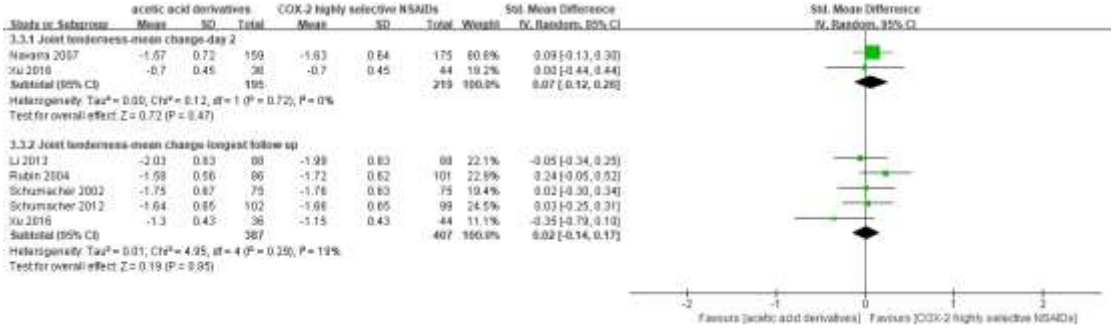
Comparison acetic acid derivatives vs. corticosteroids-im or iv



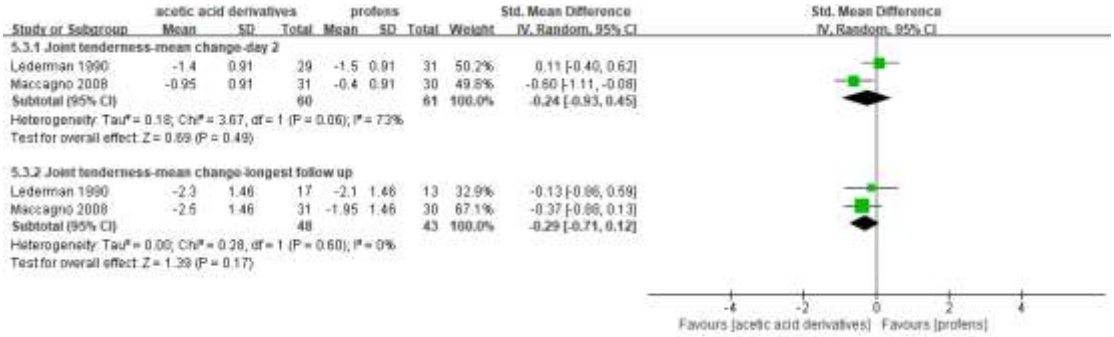
Comparison acetic acid derivatives vs. corticosteroids-po



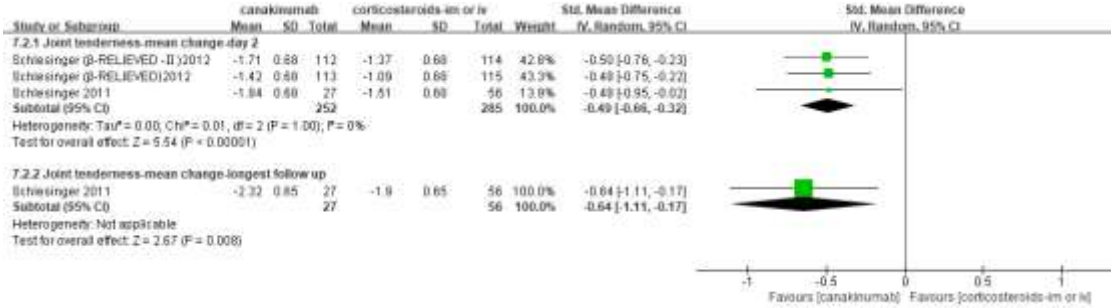
Comparison acetic acid derivatives vs. COX-2 highly selective NSAIDs



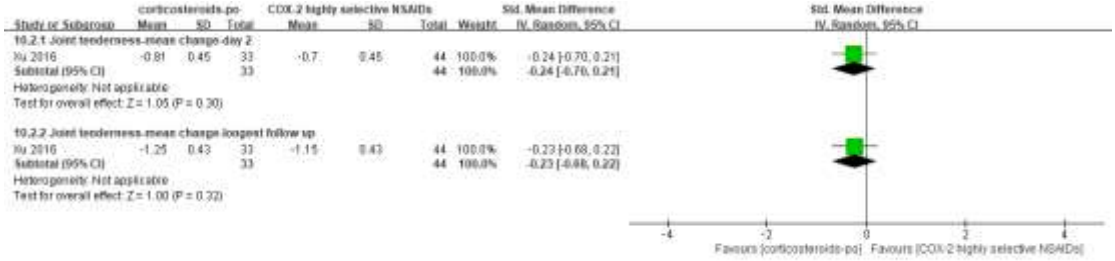
Comparison acetic acid derivatives vs. profens



Comparison canakinumab vs. corticosteroids-im or iv

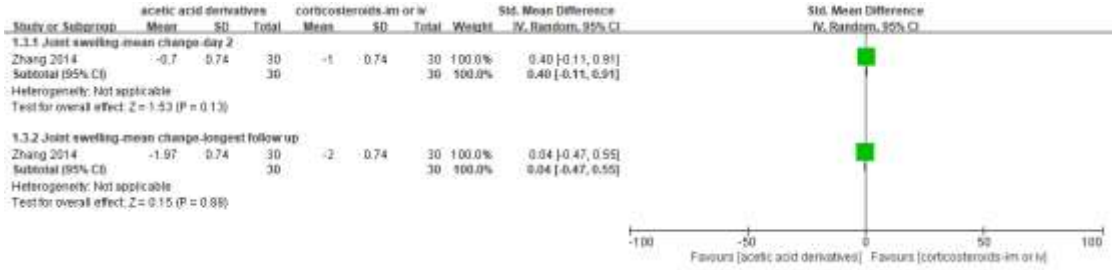


Comparison corticosteroids-po vs. COX-2 highly selective NSAIDs

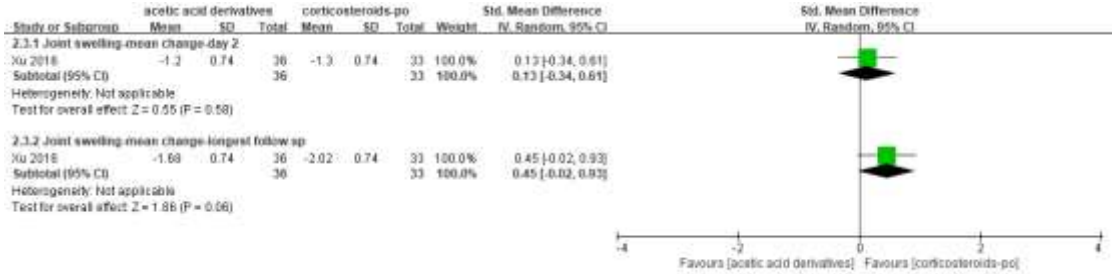


Outcome: joint swelling-mean change on Day 2 and at longest follow-up

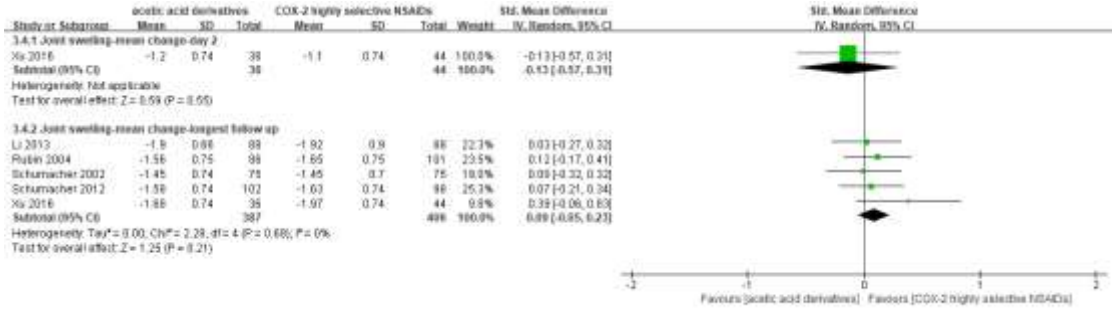
Comparison acetic acid derivatives vs. corticosteroids-im or iv



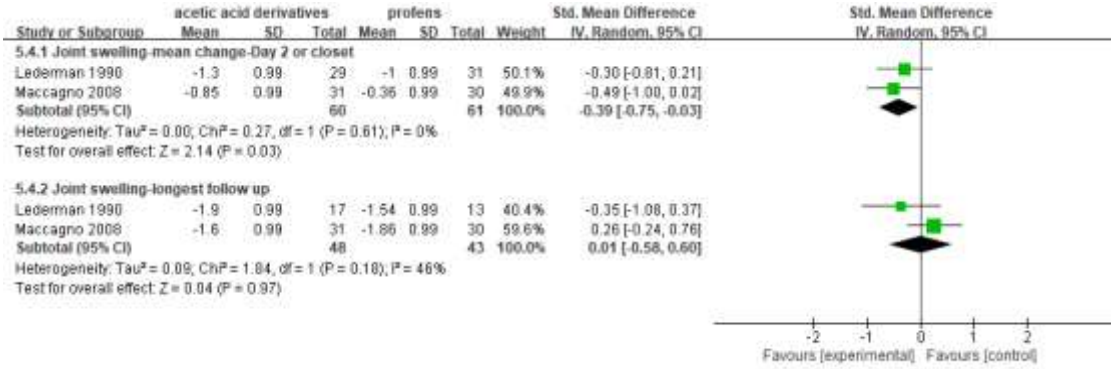
Comparison acetic acid derivatives vs. corticosteroids-po



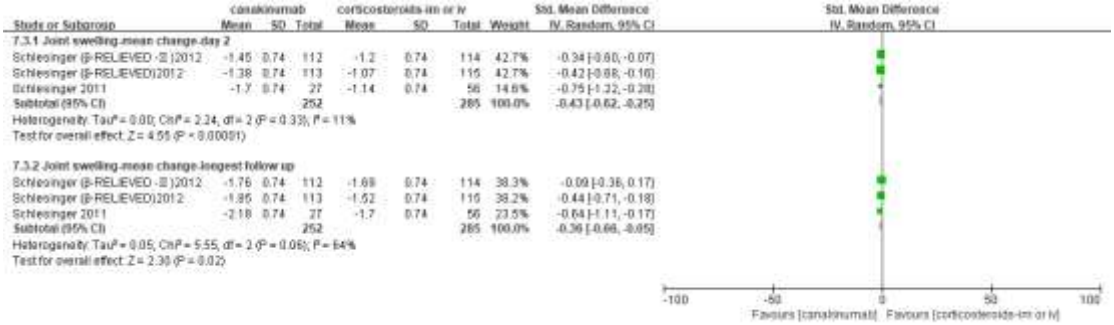
Comparison acetic acid derivatives vs. COX-2 highly selective NSAIDs



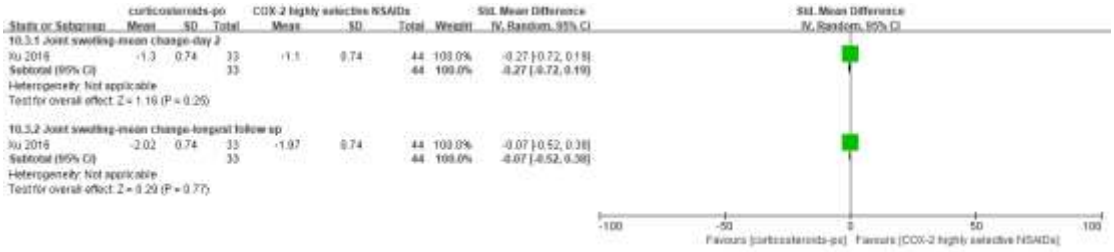
Comparison acetic acid derivatives vs. profens



Comparison canakinumab vs. corticosteroids-im or iv

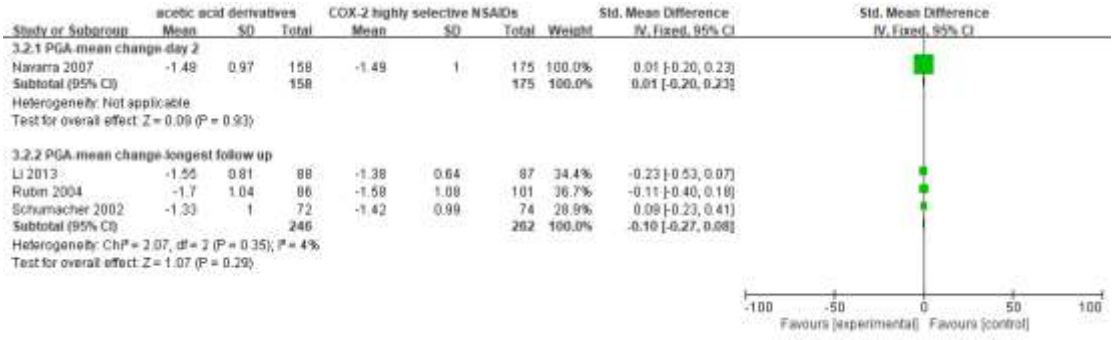


Comparison corticosteroids-po vs. COX-2 highly selective NSAIDs

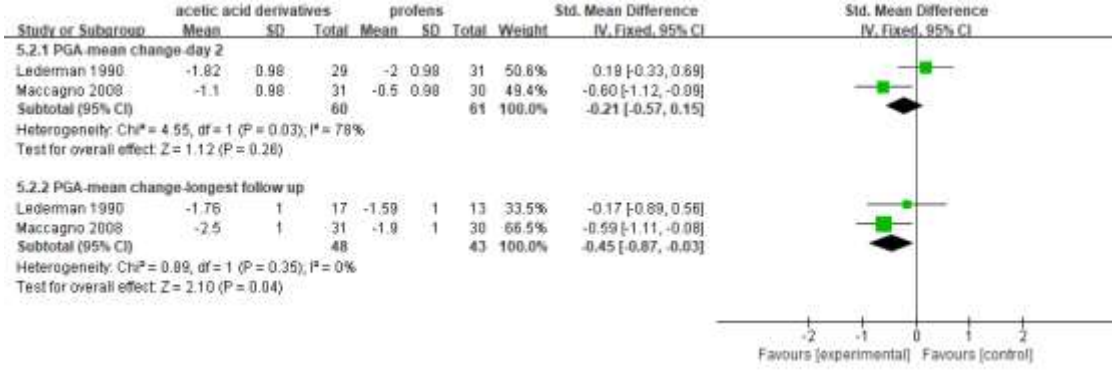


Outcome: patient global assessment-mean change on Day 2 and at longest follow-up

Comparison acetic acid derivatives vs. COX-2 highly selective NSAIDs

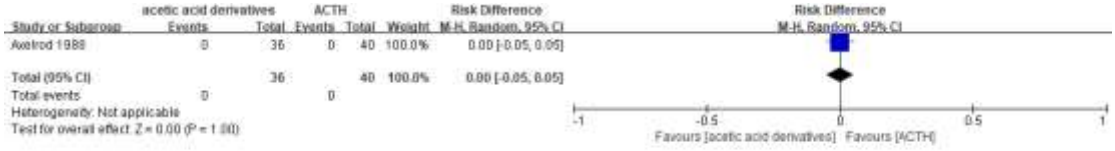


Comparison acetic acid derivatives vs. profens



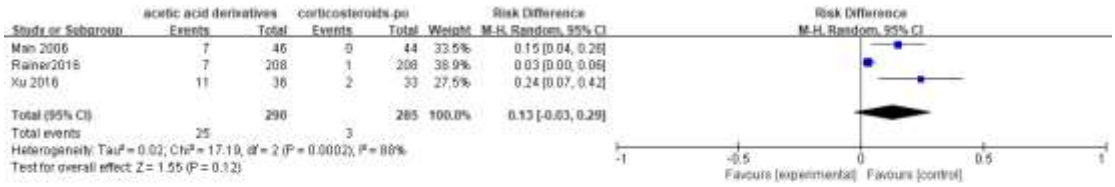
Outcome: Serious adverse events

Comparison acetic acid derivatives vs. ACTH

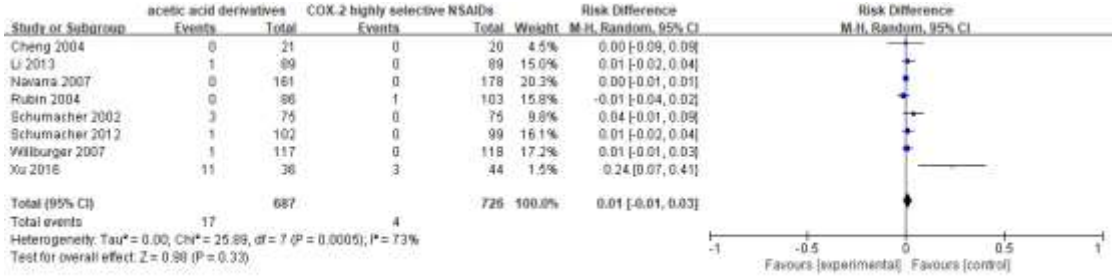


Comparison acetic acid derivatives vs. corticosteroids-im or iv

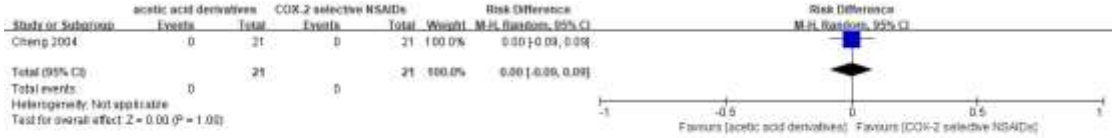
Comparison acetic acid derivatives vs. corticosteroids-po



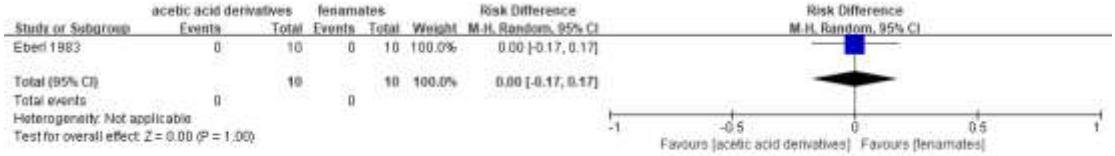
Comparison acetic acid derivatives vs. COX-2 highly selective NSAIDs



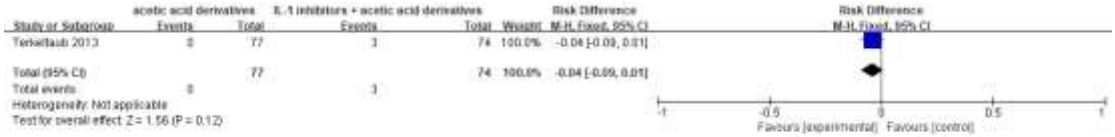
Comparison acetic acid derivatives vs. COX-2 selective NSAIDs



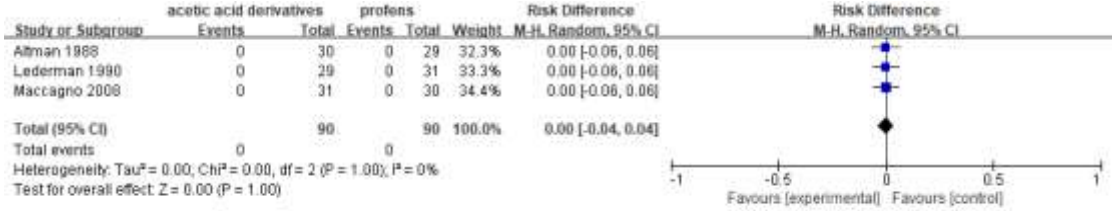
Comparison acetic acid derivatives vs. fenamates



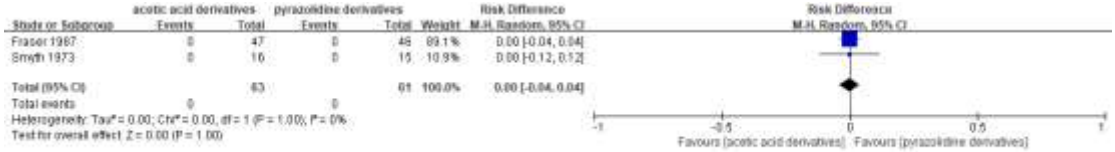
Comparison acetic acid derivatives vs. IL-1 inhibition + acetic acid derivatives



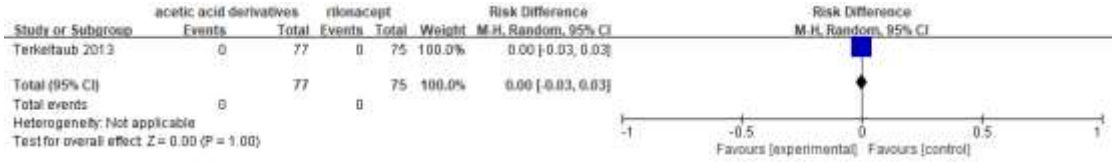
Comparison acetic acid derivatives vs. profens



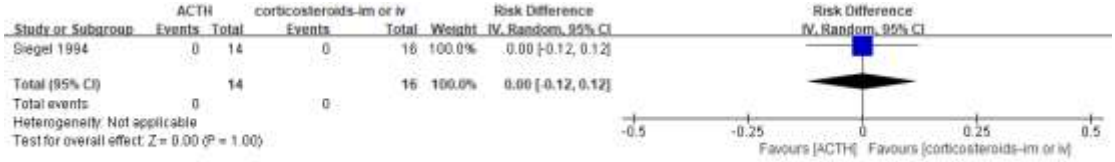
Comparison acetic acid derivatives vs. pyrazolidine derivatives



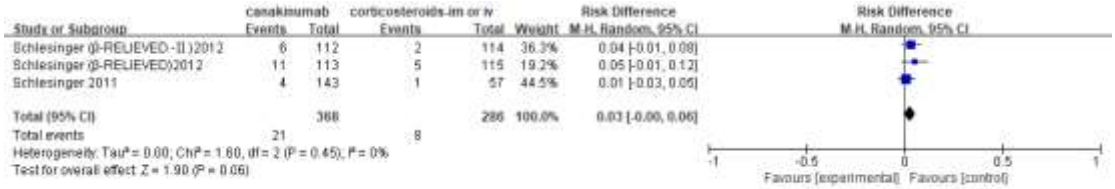
Comparison acetic acid derivatives vs. rilonacept



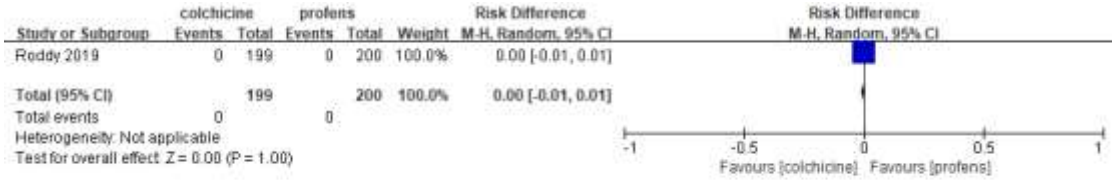
Comparison ACTH vs. corticosteroids-im or iv



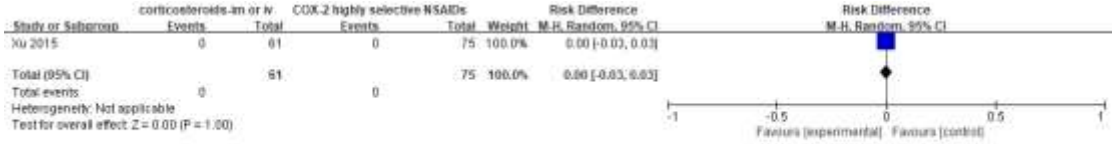
Comparison canakinumab vs. corticosteroids-im or iv



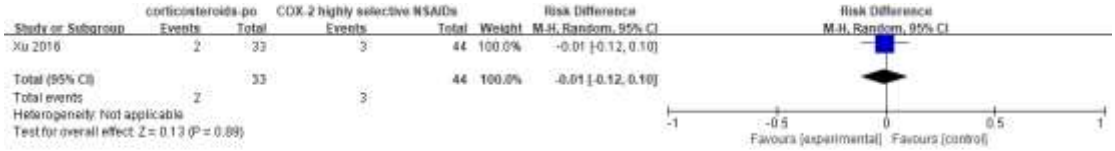
Comparison colchicine vs. profens



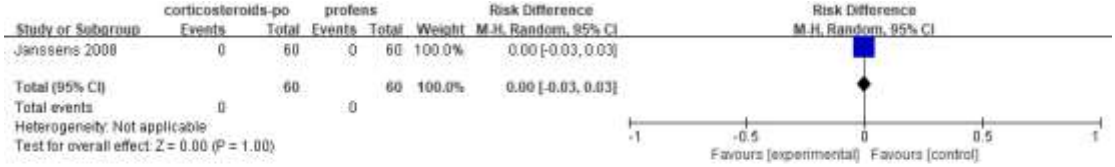
Comparison corticosteroids-im or iv vs. COX-2 highly selective NSAIDs



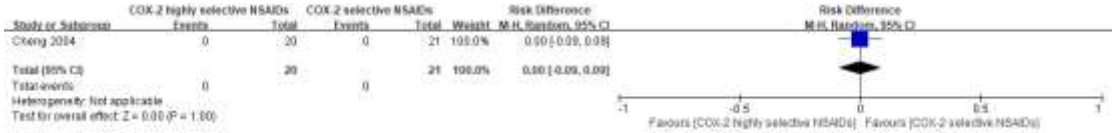
Comparison corticosteroids-po vs. COX-2 highly selective NSAIDs



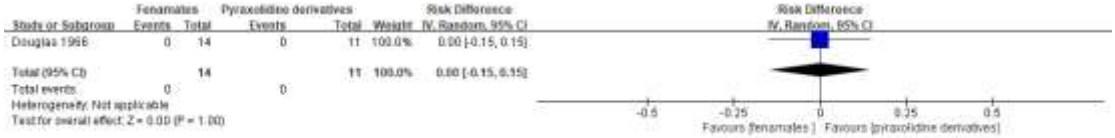
Comparison corticosteroids-po vs. profens



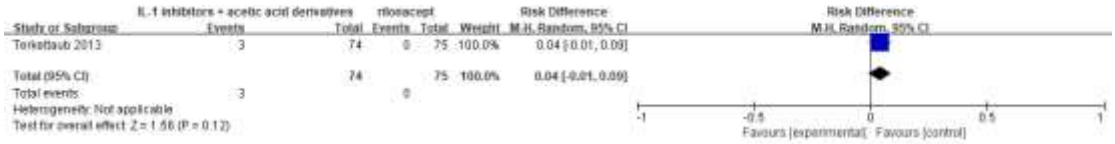
Comparison COX-2 highly selective NSAIDs vs. COX-2 selective NSAIDs



Comparison fenamates vs. pyrazolidine derivatives



Comparison IL-1 inhibition + acetic acid derivatives vs. rilonacept



Comparison pyrazolidine derivatives vs. profens