### Fever therapy in febrile adults: systematic review with meta-analyses and trial sequential analyses

**Supplementary materials** 

Authors

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### Supplementary methods

CENTRAL, BIOSIS, CINAHL, MEDLINE, Embase, LILACS, Scopus and Web of Science Core Collection were searched to identify relevant trials.<sup>1</sup> Databases were searched from their inception to July 2<sup>nd</sup> 2021.

Randomized clinical trials with adults irrespective of age, sex and comorbidities diagnosed with fever (as defined by trialists) or hyperthermia (as defined by trialists) were included. Trials had to compare fever therapy with no fever therapy (with or without placebo/ sham). Fever therapy was defined as any treatment or combination of treatments given with the intention to reduce core body temperature, e.g., physical cooling and antipyretic drugs.<sup>1</sup> Any co-intervention was allowed if the co-intervention was planned to be delivered similarly in the compared groups.

#### Primary outcomes

- All-cause mortality
- Serious adverse events, defined as any untoward medical occurrence that resulted in death, was life-threatening, required hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability or jeopardized the patient.<sup>2</sup> Expecting the reporting of serious adverse events to be heterogeneous and not strictly according to the 'International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice' (ICH-GCP) recommendations in many trials, serious adverse events were included if the trialists either: (1) used the term 'serious adverse event' but did not refer to ICH-GCP, or (2) reported the proportion of participants with an event we considered fulfilling the ICH-GCP definition. Serious adverse events were considered as any untoward medical occurrence that at any dose:
  - o results in death,
  - o is life-threatening,
  - requires inpatient hospitalization or prolongation of existing hospitalization,
  - o results in persistent or significant disability or incapacity or
  - is a congenital anomaly/birth defect

If several such events were reported, then the highest proportion reported in each trial was chosen.

#### Secondary outcomes

- Quality of life measured on any valid continuous scale
- Non-serious adverse event defined as those leading to discontinuation of the intervention or defined as 'adverse events' by the trialists. Each adverse event was, if possible, analysed separately.

#### Exploratory outcomes

- Resolution of fever (as defined by the trialists).
- Temperature change (measured by body temperature).
- Number of serious adverse events (analysed as count data).
- Number of non-serious adverse events (analysed as count data).

Two authors (JH + AC) independently reviewed and extracted the data for each trial using a data extraction sheet. Following independent data extraction, the authors conducted a meeting to discuss any discrepancies, disagreements were resolved by a third reviewer (JCJ) or by consensus. All trial authors were contacted in attempt to obtain information if there was missing or unclear data.

Assessing the risk of bias two authors (JH + AC) independently reviewed the trials using the instructions given in the *Cochrane Handbook for Systematic Reviews of Interventions* evaluating the methodology in respect of: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and other risks of bias.<sup>3</sup> The second version of the Cochrane risk-of-bias tool for randomized trials (RoB2) was used to assess risk of bias.<sup>4</sup> Each domain was assessed according to a three-step nominal scale: low risk of bias, some concerns, and high risk of bias. The overall risk of bias for a trial was classified as low risk of bias if all domains were assessed to be low risk of bias, of some concern if one or more domain were assessed as of some concern but no domain assessed as high risk of bias, and high risk of bias if any domain was assessed to be at high risk of bias. Trials at high risk of bias tend to overestimate beneficial effects and underestimate harmful effects.<sup>5-11</sup>

For dichotomous outcomes, risk ratios (RR) with 95% confidence intervals were calculated in the meta-analyses. Additionally, trial sequential analysis adjusted confidence intervals (CIs) were calculated using the trial sequential analysis program.<sup>12,13</sup> Fisher's exact test was used to calculate the risk ratio for single trial results.

We planned to handle missing data following the eight-step procedure suggested by Jakobsen *et al.* Providing that missing data constituted  $\geq 5\%$  of the overall data, the impact of missing data was evaluated through a "best-worst-case" scenario and a "worst-best-case" scenario. In the "best-worst-case" scenario it is assumed that all participants lost to follow-up in the experimental group had a beneficial outcome and those lost to follow-up in the control group had a harmful outcome and in the "worst-best-case" scenario it is assumed that all participants lost to follow-up in the experimental group had a beneficial outcome. These sensitivity analyses reveal the range of uncertainty due to missing data.<sup>14</sup>

Heterogeneity was primarily assessed through visual inspection of forest plots assessing the dispersion of trials across the combined effect estimate and secondarily through the  $I^2$  statistic.<sup>3</sup> The threshold for interpretation of the  $I^2$  statistic used the overlapping scale:

- 0 to 40%: might not be important;
- 30 to 60%: may represent moderate heterogeneity;
- 50 to 90%: may represent substantial heterogeneity;
- 75 to 100%: considerable heterogeneity

Heterogeneity was further investigated through relevant subgroup analyses. Funnel plots were used to visually assess reporting bias in meta-analyses including  $\geq 10$  trials.<sup>15,16</sup>

#### Data synthesis

Meta-analyses were performed following the *Cochrane Handbook of Systematic Reviews of Interventions*, Keus *et al* and Jakobsen *et al*. Stata version 16 (StataCorp LLC, College Station, TX, USA) was used to analyse the data.<sup>3,14,17,18</sup> Meta-analyses were performed using both fixed-effects (Mantel-Haenszel) and random-effects (DerSimonian-Laird) model to assign weight to the trials.<sup>19,20</sup> The model providing the most conservative result (highest pvalue) was chosen as the primary result, the less conservative result was considered a sensitivity analysis.<sup>18</sup> In the presence of statistical heterogeneity, a random-effects model is considered superior to a fixed-effect model but if one or two trial accounts for approximately 80 % or more of the total weight then a fixed-effect model is considered superior as a random-effects model could provide erroneous results.<sup>3</sup> The most correct and precise result is provided in the absence of heterogeneity where the two models converge and show identical results.

Multiple outcomes have major implications on the interpretation of confidence intervals and p-values due to an increased risk of false declaration of the effectiveness of an assessed intervention (type I error). To adjust the thresholds for statistical significance according to the number of outcome comparisons, a conservative approach was used dividing the pre-defined p-value threshold with the value halfway between one (no adjustment) and the number of primary outcome comparisons (Bonferroni adjustment).<sup>18</sup> A multiplicity adjusted p-value of  $\leq$  0.02 was set as threshold of statistical significance due to four primary and secondary outcomes being assessed.<sup>18</sup> The eight-step procedure suggested by Jakobsen et al was used to assess the clinical significance of the results.<sup>18</sup>

Trial sequential analyses were performed using software version 0.9.5.10 Beta (CTU, Copenhagen, Denmark) in attempt to reduce the risks of type I & II errors.<sup>13,21-30</sup> The trial sequential analysis manual was followed to estimate diversity-adjusted required information size (DARIS) and cumulative Z-curve's breach of the trial sequential monitoring boundaries.<sup>13</sup> The required information size was based on the cumulative portion of participants with events relative to all participants in the group, a relative risk reduction or increase of 25% as suggested by GRADE authors as default threshold, an alpha of 2% (p = 0.02) for all outcomes, a beta of 10% (90% power) and the diversity of the trials in the meta-analysis <sup>18,27,31</sup>. We investigated and defined the lowest effect estimate that could be confirmed or rejected using trial sequential analyses.

Subgroup analyses were performed, using Stata version 16 (StataCorp LLC, College Station, TX, USA).<sup>14</sup> Subgroup analyses were performed to investigate heterogeneity between trials and to be hypothesis-generating for further studies. Multiple analyses increase the risk of type I errors and further interpretation of the subgroup analyses results should be done with caution. We planned the following subgroup analyses:

- Comparison of different types of fever therapies
- Critically ill compared to non-critically ill participants
- Participants with infectious fever compared to non-infectious fever
- Comparison of different follow-up time points
- Comparison of different control interventions
- Comparison of different funding resources (industry funded or unknown finding/ nonindustry funding)

We performed a post hoc subgroup analysis comparing trials with a statistically significant temperature difference between the compared groups to trials with a non-significant temperature difference.

The approach proposed by the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) working group was used for rating the certainty of the evidence.<sup>32-34</sup> Five domains were assessed: risk of bias, inconsistency, indirectness, imprecision, and publication bias. The evidence was rated to be either of high certainty, moderate certainty, low certainty, or very low certainty.<sup>32-34</sup>

### **Supplementary results**

#### Quality of life

There was only one trial presenting data on quality of life. Using the EQ-5D-5L descriptive system comprising of the five dimensions of health (mobility, self-care, usual activities, pain and discomfort, and anxiety and depression) at 24, 48 and 72 hours the trial authors concluded that there was no significant difference in quality of life between paracetamol and placebo group and that further studies are needed to reveal a potential difference.<sup>35</sup>

#### Non-serious adverse events

Four trials (6 comparisons) with a total of 767 participants reported on non-serious adverse events. The included trials assessed the effects of three different fever therapy interventions: ibuprofen versus placebo <sup>36,37</sup> (2 trials), acetaminophen versus placebo <sup>38</sup> (1 trial), and sulindac versus placebo <sup>39</sup> (1 trial). 455/767 participants were hospitalised, and 453/767 were non-critically ill (Table S1). One trial included both critically ill and non-critically ill participants (314/767) (Table S1). 392/767 had infectious fever and 61/767 had non-infectious

fever (Table S1). For 120/767 participants the origin of fever was unknown (Table S1). A total of 137 trial participants out of 329 (41.6%) had a non-serious adverse event in the fever therapy group compared with 57 of 244 (23.4%) in the control group.

Meta-analysis of non-serious adverse events did not show evidence of a difference (RR 0.92; 95% CI 0.67 to 1.25;  $I^2$ =66.50%; p=0.58, 4 trials; very low certainty evidence) (Figure S20, Table 3). Quantitative measures of heterogeneity ( $I^2$ =66.50%) combined with visual inspection of the forest plot revealed signs of significant heterogeneity (Figure S20). Trial sequential analysis showed that we could neither confirm nor reject that fever therapy reduced the relative risk of non-serious adverse events by 25% (Figure S21). This outcome result was assessed as high risk of bias and the certainty of the evidence was assessed as very low (Table 3). The certainty of the evidence was downgraded three levels due to considerable risk of bias in the included trials; imprecision due to trial sequential analysis showing no crossing of trial sequential analysis monitoring boundaries, low number of participants and inconsistency due to large heterogeneity. The assessment time-points varied between trials with an interval of 1 day after randomization to 28 days after randomization.<sup>36,38</sup>

Subgroup analysis comparing different fever therapies showed evidence of a subgroup difference ( $p \le 0.01$ ) (Figure S23). When trials assessing ibuprofen were analysed separately, meta-analysis showed RR 0.76; 95% CI 0.64 to 0.91; I<sup>2</sup>=0%, 2 trials (Figure S23). When trials assessing acetaminophen were analysed separately, Fisher's exact test showed RR 4.76; 95% CI 0.24 to 96.16; 1 trial (Figure S23). When trials assessing sulindac were analysed separately, Fisher's exact test showed RR 2.18; 95% CI 1.28 to 3.70; 1 trial (Figure S23).

Subgroup analysis comparing different fever origins showed evidence of a subgroup difference ( $p \le 0.01$ ) (Figure S25). When trials assessing infectious fever were analysed separately, meta-analysis showed RR 2.23; 95% CI 1.32 to 3.75;  $I^2=0\%$ , 2 trials (Figure S25). When trials assessing non-infectious fever were analysed separately, Fisher's exact test showed RR 0.81; 95% CI 0.55 to 1.18; 1 trial (Figure S25). When trials assessing fever of unknown origin were analysed separately, Fisher's exact test showed RR 0.75; 95% CI 0.62 to 0.91; 1 trial (Figure S25).

Subgroup analysis comparing different follow-up times showed evidence of a subgroup difference ( $p \le 0.01$ ) (Figure S24). When trials with 1-day follow-up were analysed separately,

Fisher's exact test showed RR 4.76; 95% CI 0.24 to 96.16; 1 trial (Figure S26). When trials with 7-days follow-up were analysed separately, Fisher's exact test showed RR 2.18; 95% CI 1.28 to 3.70; 1 trial (Figure S26). When trials with 28-days follow-up were analysed separately, Fisher's exact test showed RR 0.75; 95% CI 0.61 to 0.91; 1 trial (Figure S26). When trials with in-hospital follow-up were analysed separately, Fisher's exact test showed RR 0.81; 95% CI 0.55 to 1.18; 1 trial (Figure S26).

None of the other subgroup analyses showed evidence of a difference (Figure S24, S27).

#### **Exploratory outcomes**

There was only one trial (two comparisons) presenting data on time until resolution of fever. The trial authors concluded that there was no significant difference in the time until resolution of fever in the three compared groups.<sup>40</sup>

Due to temperature change (fever reduction) data being presented in multiple ways not analysable in a meta-analysis, the available data are presented descriptively. The mean ( $\pm$ SD) maximal reported temperature reduction caused by antipyretics was 1.28°C ( $\pm$ 0.45) and the mean ( $\pm$ SD) maximal reported temperature reduction caused by physical cooling was 1.07 °C ( $\pm$ 0.62). Forty-six out of seventy-five comparisons showed a significantly lower temperature in the fever therapy group compared with the group without fever therapy (Table S1). The twenty-nine comparisons not presenting a significantly lower temperature in the fever therapy group consisted of 551 participants accounting for 10.7% of all participants.

### Figures

#### Figure S1: PRISMA Flow Diagram



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit <u>www.prisma-statement.org</u>.

	All-ca	ause	mortality	- Fixe	d-effects meta-analysis			
	Fever the	erapy	Contr	ol		I	Risk Ratio	Weight
Study	Survived	Died	Survived	Died	1	w	ith 95% CI	(%)
Bernard et al.	70	130	74	137		1.00	0.77 to 1.30	27.00
Diringer et al.	34	89	21	94	-	1.51	0.94 to 2.45	8.14
Gozzoli, Schöttker et al.	2	16	3	17		0.74	0.14 to 3.94	1.07
Honarmand et al.	2	8	3	7		0.67	0.14 to 3.17	1.12
Morris et al. A	1	30	1	9		0.32	0.02 to 4.70	0.57
Morris et al. B	2	28	0	9		1.61	0.08 to 30.86	0.28
Morris et al. C	2	29	0	9		1.56	0.08 to 29.92	0.29
Niven et al.	3	11	2	10		1.29	0.26 to 6.46	0.81
Promes et al.	3	37	2	19		0.79	0.14 to 4.35	0.98
Salgado et al. A	13	21	7	10		0.93	0.46 to 1.89	3.50
Salgado et al. B	11	23	6	11		0.92	0.41 to 2.05	3.00
Schortgen, Clabault et al.	43	58	48	51		0.88	0.65 to 1.19	18.17
Schulman et al.	7	37	1	37		6.05	0.78 to 46.95	0.40
Tsaganos et al.	2	39	0	39		- 4.76	0.24 to 96.16	0.19
Vasikasin et al.	0	48	0	40		0.84	0.02 to 41.25	0.20
Weinkove et al.	0	13	2	7 -		0.14	0.01 to 2.66	1.09
Yang et al.	21	13	8	23	-8-	2.39	1.25 to 4.60	3.14
Young P et al.	55	291	57	287		0.96	0.68 to 1.35	21.43
Young P.J. et al.	23	66	23	66	+	1.00	0.61 to 1.64	8.62
Overall					•	1.06	0.92 to 1.22	
Heterogeneity: I <sup>2</sup> = 0.00%, H	<sup>1<sup>2</sup></sup> = 1.00							
Test of $\theta_i = \theta_j$ : Q(18) = 17.54	l, p = 0.49							
Test of $\theta$ = 0: z = 0.81, p = 0	.42					1.1		
				1/1	28 1/8 2 32			
				Fav	ors intervention Favors control	bl		

### Figure S2: Fixed-effects meta-analysis of fever therapy versus control interventions on all-cause mortality

Fixed-effects Mantel-Haenszel model

Fixed-effects meta-analysis showed no evidence of a difference between fever therapy and control interventions on all-cause mortality (RR 1.06; 95% CI 0.92 to 1.22; p = 0.42;  $I^2 = 0$  %; 16 trials). RR: Risk ratio

CI: Confidence interval

# Figure S3: Subgroup analysis of all-cause mortality comparing different intervention types

All-cause mortality	- Subgro	oup ar	nalysis co	mparir	ng different interventions			
Fever therapy Control Risk Ratio								Weight
Study	Survived	Died	Survived	Died		w	ith 95% Cl	(%)
Ibuprofen								
Bernard et al.	70	130	74	137		1.00	0.77 to 1.30	28.52
Morris et al. A	1	30	1	9		0.32	0.02 to 4.70	0.28
Morris et al. B	2	28	0	9	·	1.61	0.08 to 30.86	0.23
Morris et al. C	2	29	0	9		1.56	0.08 to 29.92	0.23
Promes et al.	3	37	2	19		0.79	0.14 to 4.35	0.68
Heterogeneity: $\tau^2 = 0.00$ , $I^2 = 0.00\%$ , $H^2 = 1.00$					•	0.99	0.77 to 1.28	
Test of $\theta_i = \theta_j$ : Q(4) = 0.94, p = 0.92								
Acetaminophen								
Honarmand et al.	2	8	з	7		0.67	0.14 to 3.17	0.81
Tsaganos et al.	2	39	0	39		4.76	0.24 to 96.16	0.22
Vasikasin et al.	0	48	0	40		0.84	0.02 to 41.25	0.13
Weinkove et al.	0	13	2	7 -		0.14	0.01 to 2.66	0.23
Young P et al.	55	291	57	287		0.96	0.68 to 1.35	17.21
Young P.J. et al.	23	66	23	66		1.00	0.61 to 1.64	7.99
Heterogeneity: $\tau^2 = 0.00$ , $I^2 = 0.00\%$ , $H^2 = 1.00$					•	0.96	0.73 to 1.26	
Test of $\theta_i = \theta_i$ : Q(5) = 2.96, p = 0.71								
Physical cooling								
Gozzoli, Schöttker et al.	2	16	з	17		0.74	0.14 to 3.94	0.71
Schortgen, Clabault et al.	43	58	48	51		0.88	0.65 to 1.19	21.38
Yang et al.	21	13	8	23		2.39	1.25 to 4.60	4.64
Heterogeneity: $\tau^2 = 0.33$ , $I^2 = 73.71\%$ , $H^2 = 3.80$					-	1.25	0.56 to 2.76	
Test of $\theta_i = \theta_i$ : Q(2) = 7.61, p = 0.02								
Acetaminophen + physical cooling								
Niven et al.	3	11	2	10		1.29	0.26 to 6.46	0.76
Schulman et al.	7	37	1	37		6.05	0.78 to 46.95	0.47
Heterogeneity: $\tau^2 = 0.31$ , $I^2 = 26.04\%$ , $H^2 = 1.35$					-	2.44	0.55 to 10.86	
Test of $\theta_i = \theta_j$ : Q(1) = 1.35, p = 0.24								
Physical cooling + antipyretics vs antipyretics								
Diringer et al.	34	89	21	94		1.51	0.94 to 2.45	8.56
Salgado et al. A	13	21	7	10		0.93	0.46 to 1.89	3.92
Salgado et al. B	11	23	6	11		0.92	0.41 to 2.05	3.04
Heterogeneity: $\tau^2 = 0.00$ , $I^2 = 0.00\%$ , $H^2 = 1.00$					•	1.21	0.85 to 1.73	
Test of $\theta_i = \theta_j$ : Q(2) = 1.82, p = 0.40								
Overall					•	1.04	0.90 to 1.19	
Heterogeneity: $\tau^2 = 0.00$ , $I^2 = 0.00\%$ , $H^2 = 1.00$								
Test of $\theta_i = \theta_i$ : Q(18) = 17.44, p = 0.49								
Test of aroup differences; $Q_{1}(4) = 2.66$ , $p = 0.62$								
				1/15	28 1/8 2 32	-		
				Fav	vors intervention Favors control			

Random-effects DerSimonian-Laird model

Subgroup analysis comparing different intervention types showed no evidence of a subgroup difference (p = 0.62). RR: Risk ratio CI: Confidence interval

### Figure S4: Subgroup analysis of all-cause mortality comparing critically ill versus noncritically ill

All-cause mortality -	Subgroup analysis	comparing	critically ill	narticinants with	non-critically ill part	cinants
All oddoo monunty	oubgroup unuryon	b oompaning	ornouny in	purilopunto with	non ondoury in purc	orpanto

, , ,	Fever the	erany	Contr	ol			Risk Batio	Weight
Study	Survived	Died	Survived	Died		v	vith 95% CI	(%)
Critically ill								
Bernard et al.	70	130	74	137		1.00	0.77 to 1.30	28.52
Diringer et al.	34	89	21	94		1.51	0.94 to 2.45	8.56
Gozzoli, Schöttker et al.	2	16	3	17		0.74	0.14 to 3.94	0.71
Honarmand et al.	2	8	3	7		0.67	0.14 to 3.17	0.81
Niven et al.	3	11	2	10		1.29	0.26 to 6.46	0.76
Salgado et al. A	13	21	7	10	-	0.93	0.46 to 1.89	3.92
Salgado et al. B	11	23	6	11		0.92	0.41 to 2.05	3.04
Schortgen, Clabault et al.	43	58	48	51		0.88	0.65 to 1.19	21.38
Schulman et al.	7	37	1	37		- 6.05	0.78 to 46.95	0.47
Yang et al.	21	13	8	23		2.39	1.25 to 4.60	4.64
Young P et al.	55	291	57	287		0.96	0.68 to 1.35	17.21
Young P.J. et al.	23	66	23	66		1.00	0.61 to 1.64	7.99
Heterogeneity: $\tau^2 = 0.02$ , $I^2 = 19.63\%$ , $H^2 = 1.24$					•	1.07	0.89 to 1.27	
Test of $\theta_i = \theta_i$ : Q(11) = 13.69, p = 0.25								
Non-critically ill								
Promes et al.	3	37	2	19		0.79	0.14 to 4.35	0.68
Tsaganos et al.	2	39	0	39		4.76	0.24 to 96.16	0.22
Vasikasin et al.	0	48	0	40		0.84	0.02 to 41.25	0.13
Weinkove et al.	0	13	2	7		0.14	0.01 to 2.66	0.23
Heterogeneity: $\tau^{\scriptscriptstyle 2}$ = 0.00, $I^{\scriptscriptstyle 2}$ = 0.00%, $H^{\scriptscriptstyle 2}$ = 1.00					-	0.79	0.23 to 2.78	
Test of $\theta_i = \theta_j$ : Q(3) = 2.69, p = 0.44								
Both critically ill and non-critically ill								
Morris et al. A	1	30	1	9		0.32	0.02 to 4.70	0.28
Morris et al. B	2	28	0	9		- 1.61	0.08 to 30.86	0.23
Morris et al. C	2	29	0	9		- 1.56	0.08 to 29.92	0.23
Heterogeneity: $\tau^2 = 0.00$ , $I^2 = 0.00$ %, $H^2 = 1.00$						0.87	0.17 to 4.51	
Test of $\theta_i = \theta_j$ : Q(2) = 0.85, p = 0.66								
Overall					• •	1.04	0.90 to 1.19	
Heterogeneity: $\tau^2 = 0.00$ , $l^2 = 0.00\%$ , $H^2 = 1.00$								
Test of $\theta_i = \theta_j$ : Q(18) = 17.44, p = 0.49								
Test of group differences: $Q_b(2) = 0.27$ , $p = 0.87$	,							
				1/1	28 1/8 2	32		
				F	avors intervention Favors co	ntrol		

Random-effects DerSimonian-Laird model

Subgroup analysis comparing critically ill participants with non-critically ill participants showed no evidence of a subgroup difference (p = 0.87). RR: Risk ratio CI: Confidence interval I<sup>2</sup>: Measure of heterogeneity

# Figure S5: Subgroup analysis of all-cause mortality comparing infectious fever with non-infectious fever

All-cause monality - Subj	group arrais	515 60	mpanny	mecu		ious ie	vei	
Chude	Fever the	erapy	Contr	Diad			Risk Ratio	Weight
Sludy	Survived	Died	Survived	Died		w	nin 95% CI	(%)
Infectious fever								
Bernard et al.	70	130	74	137		1.00	0.77 to 1.30	28.52
Salgado et al. A	13	21	/	10		0.93	0.46 to 1.89	3.92
Salgado et al. B	11	23	6	11		0.92	0.41 to 2.05	3.04
Schortgen, Clabault et al.	43	58	48	51		0.88	0.65 to 1.19	21.38
Tsaganos et al.	2	39	0	39		- 4.76	0.24 to 96.16	0.22
Vasikasin et al.	0	48	0	40		0.84	0.02 to 41.25	0.13
Weinkove et al.	0	13	2	7 -		0.14	0.01 to 2.66	0.23
Yang et al.	21	13	8	23		2.39	1.25 to 4.60	4.64
Young P et al.	55	291	57	287		0.96	0.68 to 1.35	17.21
Heterogeneity: $\tau^2 = 0.02$ , $I^2 = 23.46\%$ , $H^2 = 1.31$					•	1.02	0.83 to 1.26	
Test of $\theta_i = \theta_j$ : Q(8) = 10.45, p = 0.23								
Non-infectious fever	0.000 M	620121	2020-01	100000211		51 (1994a)		1000000
Diringer et al.	34	89	21	94	-	1.51	0.94 to 2.45	8.56
Promes et al.	3	37	2	19		0.79	0.14 to 4.35	0.68
Young P.J. et al.	23	66	23	66	-	1.00	0.61 to 1.64	7.99
Heterogeneity: $\tau^2 = 0.00$ , $I^2 = 0.00\%$ , $H^2 = 1.00$					•	1.22	0.87 to 1.71	
Test of $\theta_i = \theta_j$ : Q(2) = 1.64, p = 0.44								
Unknown if infectious or non infectious forer								
		10	•	47		0.74	0111-001	0.74
Gozzoli, Schottker et al.	2	16	3	17		0.74	0.14 to 3.94	0.71
Honarmand et al.	2	8	3	/		0.67	0.14 to 3.17	0.81
Morris et al. A	1	30	1	9		0.32	0.02 to 4.70	0.28
Morris et al. B	2	28	0	9		1.61	0.08 to 30.86	0.23
Morris et al. C	2	29	0	9		1.56	0.08 to 29.92	0.23
Niven et al.	3	11	2	10		1.29	0.26 to 6.46	0.76
Schulman et al.	7	37	1	37		6.05	0.78 to 46.95	0.47
Heterogeneity: $\tau^2 = 0.00$ , $I^2 = 0.00\%$ , $H^2 = 1.00$					-	1.12	0.53 to 2.38	
Test of $\theta_i = \theta_j$ : Q(6) = 4.22, p = 0.65								
-								
Overall					•	1.04	0.90 to 1.19	
Heterogeneity: $\tau^2 = 0.00$ , $I^2 = 0.00\%$ , $H^2 = 1.00$								
Test of $\theta_i = \theta_j$ : Q(18) = 17.44, p = 0.49								
Test of group differences: $Q_b(2) = 0.77$ , $p = 0.68$								
				1/12	28 1/8 2 32			
				Fa	vors intervention Favors control			
Random-effects DerSimonian-Laird model								

All-cause mortality - Subgroup analysis comparing infectious fever with non-infectious fever

Subgroup analysis comparing infectious fever with non-infectious fever showed no evidence of a subgroup difference (p = 0.68).

RR: Risk ratio

CI: Confidence interval

# Figure S6: Subgroup analysis of all-cause mortality comparing different control interventions

	Fever the	erapy	Contro	ol		B	lisk Ratio	Weight
Study	Survived	Died	Survived	Died		wi	th 95% CI	(%)
Placebo								
Bernard et al.	70	130	74	137		1.00.	0.77 to 1.30	28.52
Morris et al. A	1	30	1	9		0.32.	0.02 to 4.70	0.28
Morris et al. B	2	28	0	9		1.61	0.08 to 30.86	0.23
Morris et al. C	2	29	0	9		1.56	0.08 to 29.92	0.23
Promes et al.	3	37	2	19		0.79	0.14 to 4.35	0.68
Tsaganos et al.	2	39	0	39		- 4.76	0.24 to 96.16	0.22
Vasikasin et al.	0	48	0	40		0.84	0.02 to 41.25	0.13
Weinkove et al.	0	13	2	7		0.14	0.01 to 2.66	0.23
Young P et al.	55	291	57	287		0.96	0.68 to 1.35	17.21
Heterogeneity: $\tau^2 = 0.00$ , $I^2 = 0$ .	.00%, $H^2 = 1$	1.00			•	0.98	0.80 to 1.20	
Test of $\theta_i = \theta_j$ : Q(8) = 3.69, p =	0.88							
No intervention								
Gozzoli, Schöttker et al.	2	16	3	17		0.74	0.14 to 3.94	0.71
Honarmand et al.	2	8	3	7		0.67	0.14 to 3.17	0.81
Niven et al.	3	11	2	10		1.29	0.26 to 6.46	0.76
Schortgen, Clabault et al.	43	58	48	51		0.88	0.65 to 1.19	21.38
Schulman et al.	7	37	1	37		6.05	0.78 to 46.95	0.47
Yang et al.	21	13	8	23		2.39	1.25 to 4.60	4.64
Young P.J. et al.	23	66	23	66	-	1.00	0.61 to 1.64	7.99
Heterogeneity: $\tau^2 = 0.11$ , $I^2 = 44$	4.64%, H² =	1.81			•	1.19	0.78 to 1.81	
Test of $\theta_i = \theta_j$ : Q(6) = 10.84, p =	= 0.09							
Antipyretics								
Diringer et al.	34	89	21	94	-	1.51	0.94 to 2.45	8.56
Salgado et al. A	13	21	7	10		0.93	0.46 to 1.89	3.92
Salgado et al. B	11	23	6	11		0.92	0.41 to 2.05	3.04
Heterogeneity: $\tau^2 = 0.00$ , $I^2 = 0$ .	.00%, $H^2 = 1$	1.00			•	1.21	0.85 to 1.73	
Test of $\theta_i = \theta_j$ : Q(2) = 1.82, p =	0.40							
Overall					•	1.04	0.90 to 1.19	
Heterogeneity: $\tau^2 = 0.00$ , $I^2 = 0$ .	.00%, $H^2 = 1$	1.00						
Test of $\theta_i = \theta_j$ : Q(18) = 17.44, p	= 0.49							
Test of group differences: Q <sub>b</sub> (2)	) = 1.47, p =	0.48						
				1/1	28 1/8 2 32	-		
				F	avors intervention Favors control			

All-cause mortality - Subgroup analysis comparing different control interventions

#### Random-effects DerSimonian-Laird model

Subgroup analysis comparing different control interventions (placebo, standard care and antipyretics) showed no evidence of a subgroup difference (p = 0.48). RR: Risk ratio CI: Confidence interval  $I^2$ : Measure of heterogeneity

# Figure S7: Subgroup analysis of all-cause mortality comparing trials with significantly lower temperature in fever the fever therapy group with trials with non-significantly lower temperature in the fever therapy group

All-cause mortality - Subgroup analysis comparing trials with significantly lower temperature in fever therapy group with trials which did not have a significantly lower temperature in the fever therapy group

	Fever the	erapy	Contr	ol		F	Risk Ratio	Weight
Study	Survived	Died	Survived	Died	11	w	ith 95% CI	(%)
Significantly lower temperature in fever therapy group								
Bernard et al.	70	130	74	137		1.00	0.77 to 1.30	28.52
Diringer et al.	34	89	21	94	-=-	1.51	0.94 to 2.45	8.56
Morris et al. A	1	30	1	9		0.32	0.02 to 4.70	0.28
Morris et al. B	2	28	0	9		1.61	0.08 to 30.86	0.23
Morris et al. C	2	29	0	9		1.56	0.08 to 29.92	0.23
Niven et al.	3	11	2	10		1.29	0.26 to 6.46	0.76
Promes et al.	3	37	2	19		0.79	0.14 to 4.35	0.68
Schortgen, Clabault et al.	43	58	48	51		0.88	0.65 to 1.19	21.38
Schulman et al.	7	37	1	37		6.05	0.78 to 46.95	0.47
Tsaganos et al.	2	39	0	39		- 4.76	0.24 to 96.16	0.22
Yang et al.	21	13	8	23		2.39	1.25 to 4.60	4.64
Young P et al.	55	291	57	287		0.96	0.68 to 1.35	17.21
Young P.J. et al.	23	66	23	66	+	1.00	0.61 to 1.64	7.99
Heterogeneity: $\tau^2 = 0.02$ , $I^2 = 19.73\%$ , $H^2 = 1.25$					•	1.10	0.91 to 1.33	
Test of $\theta_i = \theta_j$ : Q(12) = 14.95, p = 0.24								
Not significantly lower temperature in fever therapy group								
Gozzoli, Schöttker et al.	2	16	3	17		0.74	0.14 to 3.95	0.71
Honarmand et al.	2	8	3	7		0.67	0.14 to 3.17	0.81
Salgado et al. A	13	21	7	10		0.93	0.46 to 1.89	3.92
Salgado et al. B	11	23	6	11		0.92	0.41 to 2.05	3.04
Vasikasin et al.	0	48	0	40		0.84	0.02 to 41.25	0.13
Weinkove et al.	0	13	2	7 -		0.14	0.01 2.66	0.23
Heterogeneity: $\tau^2 = 0.00$ , $I^2 = 0.00\%$ , $H^2 = 1.00$					•	0.84	0.52 to 1.34	
Test of $\theta_i = \theta_j$ : Q(5) = 1.64, p = 0.90								
Overall					*	1.04	0.90 to 1.19	
Heterogeneity: $\tau^2 = 0.00$ , $I^2 = 0.00\%$ , $H^2 = 1.00$								
Test of $\theta_i = \theta_j$ : Q(18) = 17.44, p = 0.49								
Test of group differences: $Q_{h}(1) = 1.11$ , p = 0.29								
ant of <b>T</b> arration of a 1965 ( <b>M</b> 101 - 211 - 218)				1/1:	28 1/8 2 32	7		
				0.000				

Random-effects DerSimonian-Laird model

Subgroup analysis comparing trials with significantly lower temperature in fever the fever therapy group with trials with nonsignificantly lower temperature in the fever therapy group showed no evidence of a subgroup difference (p = 0.29). RR: Risk ratio CI: Confidence interval

Chudu	Fever the	erapy	Contr	ol		F	Risk Ratio	Weight
Study	Survived	Died	Survived	Died	0	w	101 95% 01	(%)
Pollow-up time: 1 day		10	•	47	-	0.74	0 4 4 4 - 0 0 4	0.74
Gozzoli, Schottker et al.	2	16	3	17		0.74	0.14 to 3.94	0.71
Tsaganos et al.	2	39	0	39		4.76	0.24 to 96.16	0.22
Heterogeneity: $\tau^2 = 0.19$ , $l^2 = 11.0$	)7%, H <sup>2</sup> = 1	.12				1.21	0.24 to 6.08	
Test of $\theta_i = \theta_j$ : Q(1) = 1.12, p = 0.	29							
Follow-up time: 10 days								
Honarmand et al.	2	8	3	7		0.67	0.14 to 3.17	0.81
Heterogeneity: $\tau^2 = 0.00$ , $l^2 = .%$ .	H <sup>2</sup> = .		-			0.67	0.14 to 3.17	
Test of $\theta = \theta$ ; Q(0) = -0.00, p = .								
·····, ···, ···, ····, ····, ···								
Follow-up time: 28 days								
Morris et al. A	1	30	1	9	·	0.32	0.02 to 4.70	0.28
Morris et al. B	2	28	0	9		1.61	0.08 to 30.86	0.23
Morris et al. C	2	29	0	9		1.56	0.08 to 29.92	0.23
Niven et al.	3	11	2	10		1.29	0.26 to 6.46	0.76
Yang et al.	21	13	8	23		2.39	1.25 to 4.60	4.64
Young P.J. et al.	23	66	23	66		1.00	0.61 to 1.64	7.99
Heterogeneity: $\tau^2 = 0.03$ , $l^2 = 8.67$	7%, H <sup>2</sup> = 1.	09			•	1.36	0.88 to 2.10	
Test of $\theta_1 = \theta_1$ : Q(5) = 5.47, p = 0.	36				•			
Follow-up time: 30 days								
Bernard et al.	70	130	74	137		1.00	0.77 to 1.30	28.52
Weinkove et al.	0	13	2	7 -	•	0.14	0.01 to 2.66	0.23
Heterogeneity: $\tau^2 = 0.77$ , $I^2 = 40.5$	54%, H² = 1	.68				0.67	0.14 to 3.13	
Test of $\theta_i = \theta_j$ : Q(1) = 1.68, p = 0.	19							
Follow-up time: 90 days								
Young P et al.	55	291	57	287	<b>.</b>	0.96	0.68 to 1.35	17.21
Heterogeneity: $\tau^2 = 0.00$ , $I^2 = .\%$ ,	$H^2 = .$				•	0.96	0.68 to 1.35	
Test of $\theta_{_i}=\theta_{_j}\!\!: Q(0)=0.00,p=$ .								
Follow-up time: In-hospital								
Diringer et al.	34	89	21	94	-	1.51	0.94 to 2.45	8.56
Promes et al.	3	37	2	19		0.79	0.14 to 4.35	0.68
Salgado et al. A	13	21	7	10		0.93	0.46 to 1.89	3.92
Salgado et al. B	11	23	6	11		0.92	0.41 to 2.05	3.04
Schortgen, Clabault et al.	43	58	48	51		0.88	0.65 to 1.19	21.38
Schulman et al.	7	37	1	37		6.05	0.78 to 46.95	0.47
Vasikasin et al.	0	48	0	40		0.84	0.02 to 41.25	0.13
Heterogeneity: $\tau^2 = 0.01$ , $l^2 = 9.73$	3%, H <sup>2</sup> = 1.	11			•	1.05	0.80 to 1.36	
Test of $\theta_i = \theta_j$ : Q(6) = 6.65, p = 0.	35							
Overall					1	1.04	0.90 to 1.19	
Heterogeneity: $\tau^2 = 0.00$ , $l^2 = 0.00$	$0\%, H^2 = 1.0$	00						
lest of $\theta_i = \theta_j$ : Q(18) = 17.44, p =	0.49							
Test of group differences: $Q_b(5) =$	= 2.35, p = 0	0.80		4		2		
				1/1	28 1/8 2 32			
				Fav	ors intervention Favors control			

#### Figure S8: Subgroup analysis of all-cause mortality comparing different follow-up times All-cause mortality - Subgroup analysis comparing different follow-up times

Random-effects DerSimonian-Laird model

Subgroup analysis comparing different follow-up times showed no evidence of a subgroup difference (p = 0.80). RR: Risk ratio CI: Confidence interval I<sup>2</sup>: Measure of heterogeneity

#### Figure S9: Subgroup analysis of all-cause mortality comparing trials with for profit bias with trials without for-profit bias

	for	profit	bias with	triais	with no for profit blas			
12-01 A	Fever the	erapy	Contr	ol		F	Risk Ratio	Weight
Study	Survived	Died	Survived	Died		w	ith 95% CI	(%)
For profit bias								
Diringer et al.	34	89	21	94		1.51	0.94 to 2.45	8.56
Tsaganos et al.	2	39	0	39		- 4.76	0.24 to 96.16	0.22
Heterogeneity: $\tau^2 = 0.00$ , $I^2 = 0$	.00%, H <sup>2</sup> =	1.00			•	1.56	0.97 to 2.50	
Test of $\theta_i = \theta_j$ : Q(1) = 0.54, p =	0.46							
No for profit bias								
Bernard et al.	70	130	74	137		1.00	0.77 to 1.30	28.52
Gozzoli, Schöttker et al.	2	16	3	17		0.74	0.14 to 3.94	0.71
Honarmand et al.	2	8	3	7		0.67	0.14 to 3.17	0.81
Morris et al. A	1	30	1	9		0.32	0.02 to 4.70	0.28
Morris et al. B	2	28	0	9		1.61	0.08 to 30.86	0.23
Morris et al. C	2	29	0	9		1.56	0.08 to 29.92	0.23
Niven et al.	3	11	2	10		1.29	0.26 to 6.46	0.76
Promes et al.	3	37	2	19		0.79	0.14 to 4.35	0.68
Salgado et al. A	13	21	7	10		0.93	0.46 to 1.89	3.92
Salgado et al. B	11	23	6	11		0.92	0.41 to 2.05	3.04
Schortgen, Clabault et al.	43	58	48	51		0.88	0.65 to 1.19	21.38
Schulman et al.	7	37	1	37		6.05	0.78 to 46.95	0.47
Vasikasin et al.	0	48	0	40		0.84	0.02 to 41.25	0.13
Weinkove et al.	0	13	2	7		0.14	0.01 to 2.66	0.23
Yang et al.	21	13	8	23		2.39	1.25 to 4.60	4.64
Young P et al.	55	291	57	287	-	0.96	0.68 to 1.35	17.21
Young P.J. et al.	23	66	23	66		1.00	0.61 to 1.64	7.99
Heterogeneity: $\tau^2 = 0.00$ , $I^2 = 0$	.00%, H <sup>2</sup> =	1.00			•	1.00	0.86 to 1.15	
Test of $\theta_1 = \theta_1$ : Q(16) = 13.80, p	o = 0.61							
Overall					•	1.04	0.90 to 1.19	
Heterogeneity: $\tau^2 = 0.00$ , $I^2 = 0$	0.00%, H <sup>2</sup> =	1.00						
Test of $\theta_{i} = \theta_{i}$ : Q(18) = 17.44, p	o = 0.49							
Toot of group differences: O (1	) _ 2 10 -	0.00						
rest of group unterences. Q <sub>b</sub> (1	<i>j</i> = 3.10, p	- 0.08		ا د د د		_		
				1/1 Fa	20 1/8 2 32 avors intervention Favors control			

### All-cause mortality - Subgroup analysis comparing trials with for profit bias with trials with no for profit bias

Random-effects DerSimonian-Laird model

Subgroup analysis comparing trials with for profit biased with trials with no for profit bias showed no evidence of a subgroup difference (p = 0.08). RR: Risk ratio

CI: Confidence interval

# Figure S10: Subgroup analysis of all-cause mortality comparing trials with different levels of risk of bias

All-Cause In		subgi	Oup anal	y 515 Ci	Simparing mais with time		SK UI DIAS	14/-:
Study	Fever the Survived	Died	Survived	01 Died		1 W	risk Ratio	(%)
Some concerns	Guivived	Dicu	Guivived	Dicu				(70)
Bernard et al.	70	130	74	137		1.00	0.77 to 1.30	28.52
Morris et al. A	1	30	1	9		0.32	0.02 to 4.70	0.28
Morris et al. B	2	28	0	9		1.61	0.08 to 30.86	0.23
Morris et al. C	2	29	0	9		1.56	0.08 to 29.92	0.23
Promes et al.	3	37	2	19		0.79	0.14 to 4.35	0.68
Salgado et al. A	13	21	7	10		0.93	0.46 to 1.89	3.92
Salgado et al. B	11	23	6	11		0.92	0.41 to 2.05	3.04
Tsaganos et al.	2	39	0	39		- 4.76	0.24 to 96.16	0.22
Vasikasin et al.	0	48	0	40		0.84	0.02 to 41.25	0.13
Weinkove et al.	0	13	2	7 -		0.14	0.01 to 2.66	0.23
Young P et al.	55	291	57	287		0.96	0.68 to 1.35	17.21
Young P.J. et al.	23	66	23	66	+	1.00	0.61 to 1.64	7.99
Heterogeneity: $\tau^2 = 0.00$ , $I^2 = 0.00$	= 0.00%, H <sup>2</sup>	= 1.00	1		•	0.97	0.81 to 1.16	
Test of $\theta_i = \theta_j$ : Q(11) = 3.74,	p = 0.98							
High risk of bias								
Diringer et al.	34	89	21	94	-	1.51	0.94 to 2.45	8.56
Gozzoli, Schöttker et al.	2	16	3	17		0.74	0.14 to 3.94	0.71
Honarmand et al.	2	8	3	7		0.67	0.14 to 3.17	0.81
Niven et al.	3	11	2	10		1.29	0.26 to 6.46	0.76
Schortgen, Clabault et al.	43	58	48	51		0.88	0.65 to 1.19	21.38
Schulman et al.	7	37	1	37		6.05	0.78 to 46.95	0.47
Yang et al.	21	13	8	23		2.39	1.25 to 4.60	4.64
Heterogeneity: $\tau^2 = 0.15$ , $I^2 = 0.15$	= 51.57%, H	$l^2 = 2.0$	6		•	1.34	0.85 to 2.09	
Test of $\theta_i = \theta_j$ : Q(6) = 12.39,	p = 0.05							
Overall					•	1.04	0.90 to 1.19	
Heterogeneity: $\tau^2 = 0.00$ , $I^2 = 0.00$	= 0.00%, H <sup>2</sup>	= 1.00						
Test of $\theta_i = \theta_j$ : Q(18) = 17.44	4, p = 0.49							
Test of group differences: Q	<sub>b</sub> (1) = 1.66,	p = 0.2	20			_		
				1/1	28 1/8 2 32			
				Fav	ors intervention Favors control	1		

All-cause mortality - Subgroup analysis comparing trials with different risk of bias

Random-effects DerSimonian-Laird model

Subgroup analysis comparing trials with different risk of bias showed no evidence of a subgroup difference (p = 0.20). RR: Risk ratio CI: Confidence interval

	Seri	ous adve	erse ev	rents - F	ixed-effects meta-analysis			
	Feve	r therapy	С	ontrol		F	Risk Ratio	Weight
Study	Event	No event	Event	No ever	nt	w	ith 95% CI	(%)
Bernard et al.	70	130	74	137		1.00	0.77 to 1.30	25.36
Diringer et al.	34	89	21	94	-=-	1.51	0.94 to 2.45	7.64
Gozzoli, Schöttker et al.	2	16	3	17		0.74	0.14 to 3.94	1.00
Honarmand et al.	2	8	3	7		0.67	0.14 to 3.17	1.06
Morris et al. A	6	25	2	8		0.97	0.23 to 4.06	1.06
Morris et al. B	5	25	1	8		1.50	0.20 to 11.24	0.54
Morris et al. C	4	27	1	8		1.16	0.15 to 9.13	0.55
Niven et al.	3	11	2	10		1.29	0.26 to 6.46	0.76
Promes et al.	6	34	6	15		0.52	0.19 to 1.43	2.77
Salgado et al. A	13	21	7	10	-	0.93	0.46 to 1.89	3.29
Salgado et al. B	11	23	6	11		0.92	0.41 to 2.05	2.82
Schorgen, Clabault et al.	43	58	48	51		0.88	0.65 to 1.19	17.07
Schulman et al.	7	37	1	37		6.05	0.78 to 46.95	0.38
Tsaganos et al.	2	39	0	39		4.76	0.24 to 96.16	0.18
Vasikasin et al.	0	48	0	40	2	0.84	0.02 to 41.25	0.19
Weinkove et al.	0	13	2	5		0.11	0.01 to 2.10	1.12
Yang et al.	21	13	8	23		1.37	0.89 to 2.09	5.99
Young P et al.	55	291	57	287		0.96	0.68 to 1.35	20.13
Young P.J. et al.	23	66	23	66	-	1.00	0.61 to 1.64	8.10
Overall					•	1.03	0.90 to 1.18	
Heterogeneity: I <sup>2</sup> = 0.00%, I	$H^2 = 1.00$							
Test of $\theta_i = \theta_j$ : Q(18) = 14.0	8, p = 0.7	2						
Test of $\theta = 0$ : $z = 0.41$ , $p = 0$	0.68							
				1	1/128 1/8 2 32 Favors intervention Favors control			

### Figure S11: Fixed-effects meta-analysis of fever therapy versus control interventions on serious adverse events

Fixed-effects Mantel-Haenszel model

Fixed-effects meta-analysis showed no evidence of a difference between fever control interventions and control interventions on serious adverse events (RR 1.03; 95% CI 0.90 to 1.18; p = 0.68;  $I^2 = 0$  %; 16 trials). RR: Risk ratio

CI: Confidence interval

# Figure S12: Subgroup analysis of serious adverse events comparing different intervention types

Serious adverse ever	nts - Su	bgroup ar	nalysis	compar	ing different intervention typ	bes		
	Feve	r therapy	C	ontrol		Risk Ratio		Weight
Study	Event	No event	Event	No even	ıt	W	ith 95% Cl	(%)
Ibuprofen								
Bernard et al.	70	130	74	137		1.00	0.77 to 1.30	26.22
Morris et al. A	6	25	2	8		0.97	0.23 to 4.06	0.89
Morris et al. B	5	25	1	8		1.50	0.20 to 11.24	0.45
Morris et al. C	4	27	1	8		1.16	0.15 to 9.13	0.43
Promes et al.	6	34	6	15		0.52	0.19 to 1.43	1.82
Heterogeneity: $\tau^2 = 0.00$ , $I^2 = 0.00\%$ , $H^2 = 1.00$					•	0.97	0.76 to 1.24	
Test of $\theta_i = \theta_j$ : Q(4) = 1.70, p = 0.79								
Acetaminophen								
Honarmand et al.	2	8	3	7		0.67	0.14 to 3.17	0.75
Tsaganos et al.	2	39	0	39		- 4.76	0.24 to 96.16	0.20
Vasikasin et al.	0	48	0	40		0.84	0.02 to 41.25	0.12
Weinkove et al.	0	13	2	5		0.11	0.01 to 2.10	0.21
Young P et al.	55	291	57	287		0.96	0.68 to 1.35	15.82
Young P.J. et al.	23	66	23	66	+	1.00	0.61 to 1.64	7.34
Heterogeneity: $\tau^2 = 0.00$ , $I^2 = 0.00\%$ , $H^2 = 1.00$					•	0.95	0.73 to 1.25	
Test of $\theta_i = \theta_i$ : Q(5) = 3.39, p = 0.64								
Physical cooling								
Gozzoli, Schöttker et al.	2	16	3	17		0.74	0.14 to 3.94	0.65
Schortgen, Clabault et al.	43	58	48	51		0.88	0.65 to 1.19	19.66
Yang et al.	21	13	8	23	-	1.37	0.89 to 2.09	10.07
Heterogeneity: $\tau^2 = 0.03$ , $I^2 = 30.48\%$ , $H^2 = 1.44$					•	1.04	0.74 to 1.46	
Test of $\theta_i = \theta_j$ : Q(2) = 2.88, p = 0.24								
Acetaminophen + physical cooling								
Niven et al.	3	11	2	10		1.29	0.26 to 6.46	0.70
Schulman et al.	7	37	1	37		6.05	0.78 to 46.95	0.43
Heterogeneity: $\tau^2 = 0.31$ , $I^2 = 26.04\%$ , $H^2 = 1.35$						2.44	0.55 to 10.86	
Test of $\theta_i = \theta_j$ : Q(1) = 1.35, p = 0.24								
Physical cooling + antipyretics vs antipyretics								
Diringer et al.	34	89	21	94	-	1.51	0.94 to 2.45	7.86
Salgado et al. A	13	21	7	10		0.93	0.46 to 1.89	3.60
Salgado et al. B	11	23	6	11		0.92	0.41 to 2.05	2.80
Heterogeneity: $\tau^2 = 0.00$ , $I^2 = 0.00\%$ , $H^2 = 1.00$					•	1.21	0.85 to 1.73	
Test of $\theta_i = \theta_j$ : Q(2) = 1.82, p = 0.40								
Overall					•	1.02	0.89 to 1.17	
Heterogeneity: $\tau^2 = 0.00$ , $I^2 = 0.00\%$ , $H^2 = 1.00$								
Test of $\theta_i = \theta_i$ : Q(18) = 14.07, p = 0.72								
Test of group differences; $Q_1(4) = 2.62$ , $p = 0.62$								
					1/128 1/8 2 22	_		
				F	Favors intervention Favors control	I		

Random-effects DerSimonian-Laird model

Subgroup analysis comparing different intervention types showed no evidence of a subgroup difference (p = 0.62). RR: Risk ratio CI: Confidence interval

# Figure S13: Subgroup analysis of serious adverse events comparing critically ill versus non-critically ill

Serious adverse events - Subgroup analysis comparing critically ill participants with non-critically ill participants

0	Feve	r therapy	c	ontrol	, , , ,		F	Risk Ratio	Weight
Study	Event	No event	Event	No even	nt		w	ith 95% Cl	(%)
Critically ill									
Bernard et al.	70	130	74	137			1.00	0.77 to 1.30	26.22
Diringer et al.	34	89	21	94		-8-	1.51	0.94 to 2.45	7.86
Gozzoli, Schöttker et al.	2	16	з	17		-	0.74	0.14 to 3.94	0.65
Honarmand et al.	2	8	з	7		-	0.67	0.14 to 3.17	0.75
Niven et al.	3	11	2	10			1.29	0.26 to 6.46	0.70
Salgado et al. A	13	21	7	10	-		0.93	0.46 to 1.89	3.60
Salgado et al. B	11	23	6	11	-	-	0.92	0.41 to 2.05	2.80
Schortgen, Clabault et al.	43	58	48	51			0.88	0.65 to 1.19	19.66
Schulman et al.	7	37	1	37			6.05	0.78 to 46.95	0.43
Yang et al.	21	13	8	23		-	1.37	0.89 to 2.09	10.07
Young P et al.	55	291	57	287			0.96	0.68 to 1.35	15.82
Young P.J. et al.	23	66	23	66			1.00	0.61 to 1.64	7.34
Heterogeneity: $\tau^2 = 0.00$ , $I^2 = 0.00\%$ , $H^2 = 1.00$						•	1.03	0.90 to 1.19	
Test of $\theta_i = \theta_j$ : Q(11) = 8.99, p = 0.62									
Non-critically ill									
Promes et al.	6	34	6	15			0.52	0.19 to 1.43	1.82
Tsaganos et al.	2	39	0	39	·	•	- 4.76	0.24 to 98.16	0.20
Vasikasin et al.	0	48	0	40			0.84	0.02 to 41.25	0.12
Weinkove et al.	0	13	2	5	· · · ·		0.11	0.01 to 2.10	0.21
Heterogeneity: $\tau^{\scriptscriptstyle 2}$ = 0.08, $I^{\scriptscriptstyle 2}$ = 4.80%, $H^{\scriptscriptstyle 2}$ = 1.05							0.57	0.22 to 1.52	
Test of $\theta_i = \theta_j$ : Q(3) = 3.15, p = 0.37									
Both critically ill and non-critically ill									
Morris et al. A	6	25	2	8		-	0.97	0.23 to 4.06	0.89
Morris et al. B	5	25	1	8			1.50	0.20 to 11.24	0.45
Morris et al. C	4	27	1	8		-	1.16	0.15 to 9.13	0.43
Heterogeneity: $\tau^2 = 0.00$ , $I^2 = 0.00\%$ , $H^2 = 1.00$					-		1.13	0.41 to 3.12	
Test of $\theta_i = \theta_j$ : Q(2) = 0.12, p = 0.94									
Overall						1	1.02	0.89 to 1.17	
Heterogeneity: $\tau^2 = 0.00$ , $I^2 = 0.00\%$ , $H^2 = 1.00$									
Test of $\theta_i = \theta_j$ : Q(18) = 14.07, p = 0.72									
Test of group differences: $Q_{b}(2) = 1.41$ , $p = 0.49$	)								
					1/128 1/8	2 32			
					Favors intervention	Favors control			

Random-effects DerSimonian-Laird model

Subgroup analysis comparing critically ill with non-critically ill showed no evidence of a subgroup difference (p = 0.49). RR: Risk ratio CI: Confidence interval

# Figure S14: Subgroup analysis of serious adverse events comparing infectious fever with non-infectious fever

Serious adverse events - Su	ubgroup	analysis	compa	aring infe	ectious fever with non-ir	fectious	s fever	
	Feve	r therapy	С	ontrol			Risk Ratio	Weight
Study	Event	No event	Event	No event		v	ith 95% CI	(%)
Infectious fever								
Bernard et al.	70	130	74	137		1.00	0.77 to 1.30	26.22
Salgado et al. A	13	21	7	10	-	0.93	0.46 to 1.89	3.60
Salgado et al. B	11	23	6	11		0.92	0.41 to 2.05	2.80
Schortgen, Clabault et al.	43	58	48	51		0.88	0.65 to 1.19	19.66
Tsaganos et al.	2	39	0	39			0.24 to 96.16	0.20
Vasikasin et al.	0	48	0	40	-	- 0.84	0.02 to 41.25	0.12
Weinkove et al.	0	13	2	5		0.11	0.01 to 2.10	0.21
Yang et al.	21	13	8	23	-	1.37	0.89 to 2.09	10.07
Young P et al.	55	291	57	287		0.96	0.68 to 1.35	15.82
Heterogeneity: $\tau^2 = 0.00$ , $I^2 = 0.00\%$ , $H^2 = 1.00$					•	0.99	0.85 to 1.15	
Test of $\theta_i = \theta_j$ : Q(8) = 6.07, p = 0.64								
Non-infectious fever								
Diringer et al.	34	89	21	94	-	1.51	0.94 to 2.45	7.86
Promes et al.	6	34	6	15		0.52	0.19 to 1.43	1.82
Young P.J. et al.	23	66	23	66	+	1.00	0.61 to 1.64	7.34
Heterogeneity: τ² = 0.09, l² = 48.79%, H² = 1.95					•	1.06	0.65 to 1.73	
Test of $\theta_i = \theta_j$ : Q(2) = 3.91, p = 0.14								
Unknown if infectious or non-infectious fever								
Gozzoli. Schöttker et al.	2	16	3	17		0.74	0.14 to 3.94	0.65
Honarmand et al.	2	8	3	7		0.67	0.14 to 3.17	0.75
Morris et al. A	6	25	2	8		0.97	0.23 to 4.06	0.89
Morris et al. B	5	25	1	8		1.50	0.20 to 11.24	0.45
Morris et al. C	4	27	1	8		1.16	0.15 to 9.13	0.43
Niven et al.	3	11	2	10		1.29	0.26 to 6.46	0.70
Schulman et al.	7	37	1	37		- 6.05	0.78 to 46.95	0.43
Heterogeneity: $\tau^2 = 0.00$ , $I^2 = 0.00\%$ , $H^2 = 1.00$					•	1.17	0.61 to 2.24	
Test of $\theta_i = \theta_j$ : Q(6) = 3.39, p = 0.76								
Overall						1 02	0.89 to 1.17	
Heterogeneity: $\tau^2 = 0.00$ $l^2 = 0.00\%$ $H^2 = 1.00$						1.02	0.00 10 1.17	
Test of $\theta_i = \theta_i$ : Q(18) = 14.07, p = 0.72								
Test of group differences: $Q_{_b}(2) = 0.29$ , p = 0.86								
				1 Fa	/128 1/8 2 3 avors intervention Favors co	2 ntrol		
Random-effects DerSimonian-Laird model								

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Subgroup analysis comparing infectious fever with non-infectious fever showed no evidence of a subgroup difference (p = 0.86).

RR: Risk ratio CI: Confidence interval

# Figure S15: Subgroup analysis of serious adverse events comparing different control interventions

	Feve	therapy	C	ontrol		F	Risk Ratio	Weight
Study	Event	No event	Event	No even	t	w	ith 95% Cl	(%)
Placebo								
Bernard et al.	70	130	74	137		1.00	0.77 to 1.30	26.22
Morris et al. A	6	25	2	8		0.97	0.23 to 4.06	0.89
Morris et al. B	5	25	1	8		1.50	0.20 to 11.24	0.45
Morris et al. C	4	27	1	8		1.16	0.15 to 9.13	0.43
Promes et al.	6	34	6	15		0.52	0.19 to 1.43	1.82
Tsaganos et al.	2	39	0	39		- 4.76	0.24 to 96.16	0.20
Vasikasin et al.	0	48	0	40		0.84	0.02 to 41.25	0.12
Weinkove et al.	0	13	2	5		0.11	0.01 to 2.10	0.21
Young P et al.	55	291	57	287		0.96	0.68 to 1.35	15.82
Heterogeneity: $\tau^2 = 0.00$ , $I^2 = 0$ .	.00%, H²	= 1.00			•	0.96	0.79 to 1.17	
Test of $\theta_i = \theta_j$ : Q(8) = 4.85, p =	0.77							
No intervention								
Gozzoli, Schöttker et al.	2	16	3	17		0.74	0.14 to 3.94	0.65
Honarmand et al.	2	8	3	7		0.67	0.14 to 3.17	0.75
Niven et al.	3	11	2	10		1.29	0.26 to 6.46	0.70
Schortgen, Clabault et al.	43	58	48	51		0.88	0.65 to 1.19	19.66
Schulman et al.	7	37	1	37		6.05	0.78 to 46.95	0.43
Yang et al.	21	13	8	23	-	1.37	0.89 to 2.09	10.07
Young P.J. et al.	23	66	23	66		1.00	0.61 to 1.64	7.34
Heterogeneity: $\tau^2 = 0.00$ , $I^2 = 2$ .	32%, H²	= 1.02			•	1.03	0.83 to 1.29	
Test of $\theta_i = \theta_j$ : Q(6) = 6.14, p =	0.41							
Antipyretics								
Diringer et al.	34	89	21	94	-	1.51	0.94 to 2.45	7.86
Salgado et al. A	13	21	7	10		0.93	0.46 to 1.89	3.60
Salgado et al. B	11	23	6	11	-	0.92	0.41 to 2.05	2.80
Heterogeneity: $\tau^2 = 0.00$ , $I^2 = 0.00$	.00%, H <sup>2</sup>	= 1.00			•	1.21	0.85 to 1.73	
Test of $\theta_i = \theta_j$ : Q(2) = 1.82, p =	0.40							
Overall					•	1.02	0.89 to 1.17	
Heterogeneity: $\tau^2 = 0.00$ , $I^2 = 0.00$	.00%, H²	= 1.00						
Test of $\theta_i = \theta_j$ : Q(18) = 14.07, p	= 0.72							
Test of group differences: Q <sub>b</sub> (2)	= 1.26,	0 = 0.53						
					1/128 1/8 2 32	-		
					Favors intervention Favors control			

Serious adverse events - Subgroup analysis comparing different control interventions

Random-effects DerSimonian-Laird model

Subgroup analysis comparing different interventions showed no evidence of a subgroup difference (p = 0.53). RR: Risk ratio CI: Confidence interval

# Figure S16: Subgroup analysis of serious adverse events comparing trials with significantly lower temperature in fever the fever therapy group with trials with non-significantly lower temperature in the fever therapy group

	Feve	therapy	С	ontrol	1,7,5,1	F	Risk Ratio	Weight
Study	Event	No event	Event	No even	nt	w	ith 95% CI	(%)
Significantly lower temperature in fever therapy group								
Bernard et al.	70	130	74	137		1.00	0.77 to 1.30	26.22
Diringer et al.	34	89	21	94		1.51	0.94 to 2.45	7.86
Morris et al. A	6	25	2	8		0.97	0.23 to 4.06	0.89
Morris et al. B	5	25	1	8		1.50	0.20 to 11.24	0.45
Morris et al. C	4	27	1	8		1.16	0.15 to 9.13	0.43
Niven et al.	з	11	2	10		1.29	0.26 to 6.46	0.70
Promes et al.	6	34	6	15		0.52	0.19 to 1.43	1.82
Schortgen, Clabault et al.	43	58	48	51		0.88	0.65 to 1.19	19.66
Schulman et al.	7	37	1	37		6.05	0.78 to 46.95	0.43
Tsaganos et al.	2	39	0	39		- 4.76	0.24 to 96.16	0.20
Yang et al.	21	13	8	23	-	1.37	0.89 to 2.09	10.07
Young P et al.	55	291	57	287		0.96	0.68 to 1.35	15.82
Young P.J. et al.	23	66	23	66	+	1.00	0.61 to 1.64	7.34
Heterogeneity: $\tau^2 = 0.00$ , $I^2 = 0.00\%$ , $H^2 = 1.00$					•	1.04	0.90 to 1.20	
Test of $\theta_i = \theta_j$ : Q(12) = 11.26, p = 0.51								
Not significantly lower temperature in fever therapy group								
Gozzoli, Schöttker et al.	2	16	3	17		0.74	0.14 to 3.94	0.65
Honarmand et al.	2	8	3	7		0.67	0.14 to 3.17	0.75
Salgado et al. A	13	21	7	10		0.93	0.46 to 1.89	3.60
Salgado et al. B	11	23	6	11		0.92	0.41 to 2.05	2.80
Vasikasin et al.	0	48	0	40		0.84	0.02 to 41.25	0.12
Weinkove et al.	0	13	2	5		0.11	0.01 to 2.10	0.21
Heterogeneity: $\tau^2 = 0.00$ , $I^2 = 0.00\%$ , $H^2 = 1.00$					•	0.83	0.52 to 1.34	
Test of $\theta_i = \theta_j$ : Q(5) = 2.03, p = 0.84								
Overall					•	1.02 [	0.89 to 1.17	
Heterogeneity: $\tau^2 = 0.00$ , $I^2 = 0.00\%$ , $H^2 = 1.00$								
Test of $\theta_i = \theta_j$ : Q(18) = 14.07, p = 0.72								
Test of group differences: $Q_b(1) = 0.77$ , p = 0.38						_		
				5	1/128 1/8 2 32 Favors intervention Favors control			

Serious adverse events - Subgroup analysis comparing trials with significantly lower temperature in fever therapy group with trials which did not have significantly lower temperature in the fever therapy group

Random-effects DerSimonian-Laird model

Subgroup analysis comparing trials with significantly lower temperature in fever the fever therapy group with trials with nonsignificantly lower temperature in the fever therapy group showed no evidence of a subgroup difference (p = 0.38). RR: Risk ratio CI: Confidence interval

# Figure S17: Subgroup analysis of serious adverse events comparing different follow-up times

Serious a	adverse e	events - S	ubgrou	ıp analys	is comparing different follow	v-up ti	mes	
	Feve	r therapy	С	ontrol		F	Risk Ratio	Weight
Study	Event	No event	Event	No event	1	w	vith 95% Cl	(%)
Follow-up time: 1 day								
Gozzoli, Schöttker et al.	2	16	3	17		0.74	0.14 to 3.94	0.65
Tsaganos et al.	2	39	0	39		- 4.76	0.24 to 96.16	0.20
Heterogeneity: $\tau^2 = 0.19$ , $I^2 = 1$	1.07%, H <sup>2</sup>	= 1.12				1.21	0.24 to 6.08	
Test of $\theta_i = \theta_j$ : Q(1) = 1.12, p =	0.29							
Follow-up time: 10 days								
Honarmand et al.	2	8	3	7		0.67	0.14 to 3.17	0.75
Heterogeneity: $\tau^2 = 0.00$ , $I^2 = .6$	%, H² = .					0.67	0.14 to 3.17	
Test of $\theta_i = \theta_j$ : Q(0) = -0.00, p =	=.							
Follow-up time: 28 days								
Morris et al. A	6	25	2	8		0.97	0.23 to 4.06	0.89
Morris et al. B	5	25	1	8		1.50	0.20 to 11.24	0.45
Morris et al. C	4	27	1	8		1.16	0.15 to 9.13	0.43
Niven et al.	3	11	2	10		1.29	0.26 to 6.46	0.70
Yang et al.	21	13	8	23	-	1.37	0.89 to 2.09	10.07
Young P.J. et al.	23	66	23	66	-	1.00	0.61 to 1.64	7.34
Heterogeneity: $\tau^2 = 0.00$ , $I^2 = 0$	.00%, H <sup>2</sup> =	1.00			•	1.19	0.88 to 1.62	
Test of $\theta_i = \theta_j$ : Q(5) = 1.01, p =	0.96							
Follow-up time: 30 days								
Bernard et al.	70	130	74	137		1.00	0.77 to 1.30	26.22
Weinkove et al.	0	13	2	5		0.11	0.01 to 2.10	0.21
Heterogeneity: $\tau^2 = 1.24$ , $I^2 = 5$	2.69%, H <sup>2</sup>	= 2.11				0.56	0.09 to 3.66	
Test of $\theta_i = \theta_j$ : Q(1) = 2.11, p =	0.15							
Follow-up time: 90 days								
Young P et al.	55	291	57	287		0.96	0.68 to 1.35	15.82
Heterogeneity: $\tau^2 = 0.00$ , $I^2 = .6$	%, H² = .				•	0.96	0.68 to 1.35	
Test of $\theta_i = \theta_j$ : Q(0) = 0.00, p =								
Follow-up time: In-hospital								
Diringer et al.	34	89	21	94		1.51	0.94 to 2.45	7.86
Promes et al.	6	34	6	15		0.52	0.19 to 1.43	1.82
Salgado et al. A	13	21	7	10		0.93	0.46 to 1.89	3.60
Salgado et al. B	11	23	6	11		0.92	0.41 to 2.05	2.80
Schortgen, Clabault et al.	43	58	48	51		0.88	0.65 to 1.19	19.66
Schulman et al.	7	37	1	37		6.05	0.78 to 46.95	0.43
Vasikasin et al.	0	48	0	40		0.84	0.02 to 41.25	0.12
Heterogeneity: $\tau^2 = 0.04$ , $I^2 = 2$	6.84%, H <sup>2</sup>	= 1.37			•	1.02	0.74 to 1.39	
Test of $\theta_i = \theta_j$ : Q(6) = 8.20, p =	0.22							
Overall						1.02	0.89 to 1.17	
Heterogeneity: $\tau^2 = 0.00$ , $I^2 = 0$	.00%, H <sup>2</sup> =	1.00						
Test of $\theta_i = \theta_j$ : Q(18) = 14.07, p	0 = 0.72							
Test of group differences: Q <sub>b</sub> (5	) = 1.80, p	= 0.88			· · · · · · · · · · · · · · · · · · ·	2		
					1/128 1/8 2 32 Favors intervention Favors control			

Random-effects DerSimonian-Laird model

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Subgroup analysis comparing different follow-up times showed no evidence of a subgroup difference (p = 0.88). RR: Risk ratio CI: Confidence interval I<sup>2</sup>: Measure of heterogeneity

### Figure S18: Subgroup analysis of serious adverse events comparing trials with for profit bias with trials without for-profit bias

Serious	adverse events - Subgroup analysis comparing trials with	
	for profit bias with trials with no for profit bias	

	Risk Ratio		Weiaht					
Study	Event	No event	Event	No even	t	w	ith 95% CI	(%)
For profit bias								
Diringer et al.	34	89	21	94		1.51	0.94 to 2.45	7.86
Tsaganos et al.	2	39	0	39		4.76	0.24 to 96.16	0.20
Heterogeneity: $\tau^2 = 0.00$ , $I^2 =$	0.00%,	$H^2 = 1.00$			•	1.56	0.97 to 2.50	
Test of $\theta_i = \theta_j$ : Q(1) = 0.54, p	= 0.46							
No for profit bias								
Bernard et al.	70	130	74	137	_	1.00	0.77 to 1.30	26.22
Gozzoli, Schöttker et al.	2	16	3	17		0.74	0.14 to 3.94	0.65
Honarmand et al.	2	8	3	7		0.67	0.14 to 3.17	0.75
Morris et al. A	6	25	2	8		0.97	0.23 to 4.06	0.89
Morris et al. B	5	25	1	8		1.50	0.20 to 11.24	0.45
Morris et al. C	4	27	1	8		1.16	0.15 to 9.13	0.43
Niven et al.	3	11	2	10		1.29	0.26 to 6.46	0.70
Promes et al.	6	34	6	15		0.52	0.19 to 1.43	1.82
Salgado et al. A	13	21	7	10		0.93	0.46 to 1.89	3.60
Salgado et al. B	11	23	6	11		0.92	0.41 to 2.05	2.80
Schortgen, Clabault et al.	43	58	48	51		0.88	0.65 to 1.19	19.66
Schulman et al.	7	37	1	37		6.05	0.78 to 46.95	0.43
Vasikasin et al.	0	48	0	40		0.84	0.02 to 41.25	0.12
Weinkove et al.	0	13	2	5		0.11	0.01 to 2.10	0.21
Yang et al.	21	13	8	23	-	1.37	0.89 to 2.09	10.07
Young P et al.	55	291	57	287		0.96	0.68 to 1.35	15.82
Young P.J. et al.	23	66	23	66	-	1.00	0.61 to 1.64	7.34
Heterogeneity: $\tau^2 = 0.00$ , $l^2 =$	0.00%,	H <sup>2</sup> = 1.00			•	0.98	0.85 to 1.13	
Test of $\theta_{i} = \theta_{i}$ : Q(16) = 10.20	, p = 0.8	6						
Overall					•	1.02	0.89 to 1.17	
Heterogeneity: $\tau^2 = 0.00$ , $I^2 =$	0.00%,	H <sup>2</sup> = 1.00						
Test of $\theta_i = \theta_j$ : Q(18) = 14.07	, p = 0.7	2						
Test of group differences: Q <sub>b</sub>	(1) = 3.3	33, p = 0.07						
					1/128 1/8 2 32	•		
					Favors intervention Favors control			

Random-effects DerSimonian-Laird model

Subgroup analysis comparing trials with for profit bias with trials without for profit showed no evidence of a subgroup difference (p = 0.07). RR: Risk ratio CI: Confidence interval  $I^2$ : Measure of heterogeneity

# Figure S19: Subgroup analysis of serious adverse events comparing trials with different levels of risk of bias

	Feve	r therapy	g. o u p C	ontrol	oompaning male mar and	F	Risk Batio	Weight
Study	Event	No event	Event	No event		w	ith 95% Cl	(%)
Some concerns								
Bernard et al.	70	130	74	137		1.00	0.77 to 1.30	26.22
Morris et al. A	6	25	2	8		0.97	0.23 to 4.06	0.89
Morris et al. B	5	25	1	8		1.50	0.20 to 11.24	0.45
Morris et al. C	4	27	1	8		1.16	0.15 to 9.13	0.43
Promes et al.	6	34	6	15		0.52	0.19 to 1.43	1.82
Salgado et al. A	13	21	7	10		0.93	0.46 to 1.89	3.60
Salgado et al. B	11	23	6	11		0.92	0.41 to 2.05	2.80
Tsaganos et al.	2	39	0	39		4.76	0.24 to 96.16	0.20
Vasikasin et al.	0	48	0	40		0.84	0.02 to 41.25	0.12
Weinkove et al.	0	13	2	5		0.11	0.01 to 2.10	0.21
Young P et al.	55	291	57	287		0.96	0.68 to 1.35	15.82
Young P.J. et al.	23	66	23	66		1.00	0.61 to 1.64	7.34
Heterogeneity: $\tau^2 = 0.00$ , $l^2 =$	0.00%,	H <sup>2</sup> = 1.00			•	0.96	0.81 to 1.14	
Test of $\theta_i = \theta_j$ : Q(11) = 4.90,	p = 0.94							
High risk of bias								
Diringer et al.	34	89	21	94	-=-	1.51	0.94 to 2.45	7.86
Gozzoli, Schöttker et al.	2	16	3	17		0.74	0.14 to 3.94	0.65
Honarmand et al.	2	8	3	7		0.67	0.14 to 3.17	0.75
Niven et al.	3	11	2	10		1.29	0.26 to 6.46	0.70
Schortgen, Clabault et al.	43	58	48	51		0.88	0.65 to 1.19	19.66
Schulman et al.	7	37	1	37		6.05	0.78 to 46.95	0.43
Yang et al.	21	13	8	23	-	1.37	0.89 to 2.09	10.07
Heterogeneity: $\tau^2 = 0.04$ , $I^2 =$	25.77%	H <sup>2</sup> = 1.35			•	1.17	0.87 to 1.57	
Test of $\theta_i = \theta_j$ : Q(6) = 8.08, p	= 0.23							
Overall					•	1.02	0.89 to 1.17	
Heterogeneity: $\tau^2 = 0.00$ , $I^2 =$	0.00%,	$H^2 = 1.00$						
Test of $\theta_i = \theta_j$ : Q(18) = 14.07	, p = 0.72	2						
Test of group differences: Q <sub>b</sub>	(1) = 1.23	3, p = 0.27						
				1	/128 1/8 2 32			
				Fa	avors intervention Favors control			

Serious adverse events - Subgroup analysis comparing trials with different risk of bias

Random-effects DerSimonian-Laird model

Subgroup analysis comparing trials with different risk of bias showed no evidence of a subgroup difference (p = 0.27). RR: Risk ratio

CI: Confidence interval

	Nor	-serious	advers	se event	s - Rano	dom-effe	ects m	eta-a	nalys	sis	
	Feve	r therapy	С	ontrol					F	Risk Ratio	Weight
Study	Event	No event	Event	No event					w	ith 95% Cl	(%)
Ebel et al.	37	119	17	139					2.18	1.28 to 3.70	15.39
Morris et al. A	21	10	9	1	-				0.75	0.55 to 1.04	21.70
Morris et al. B	20	10	8	1					0.75	0.53 to 1.06	20.95
Morris et al. C	21	10	8	1	-=				0.76	0.55 to 1.07	21.18
Promes et al.	23	17	15	6	-				0.81	0.55 to 1.18	19.77
Tsaganos et al.	2	39	0	39		•			4.76	0.24 to 96.16	1.01
Overall					•	•			0.92	0.67 to 1.25	
Heterogeneity: τ <sup>2</sup>	= 0.09, l <sup>2</sup>	<sup>e</sup> = 66.50%,	H <sup>2</sup> = 2.9	8							
Test of $\theta_i = \theta_i$ : Q(5)	5) = 14.92	2, p = 0.01									
Test of $\theta = 0$ : $z = 0$	-0.55, p =	= 0.58									
					1/4 1	4	16	64			
				Favors inte	rvention	Favors co	ontrol				

### Figure S20: Random-effects meta-analysis of fever therapy versus control interventions on non-serious adverse events

Random-effects DerSimonian-Laird model

Random-effects meta-analysis showed no evidence of a difference between fever control interventions and control interventions on non-serious adverse events (RR 0.92; 95% CI 0.67 to 1.25; p = 0.58;  $I^2 = 66.50$  %; four trials). RR: Risk ratio

CI: Confidence interval



Figure S21: Trial sequential analysis of fever therapy versus control interventions on non-serious adverse events

Two-sided trial sequential analysis graph of fever control interventions versus control interventions on non-serious adverse events in 4 trials. The diversity-adjusted required information size (DARIS) was calculated based on an all-cause mortality proportion in the control group (Pc) of 23.4 %, relative risk reduction (RRR) of 25 % in the experimental group, type I error (alpha) of 2 %, and type II error (beta) of 10 % (90% power). Diversity was 81 %. The required information size was calculated to be 13158 participants. The cumulative Z-curve (blue line) did not cross the trial sequential monitoring boundaries for neither benefit nor harm. The cumulative Z-curve did not cross the inner-wedge futility line (red outward sloping lines). The dark red lines show the conventional boundary (alpha 5%).

#### Figure S22: Fixed-effects meta-analysis of fever therapy versus control interventions on non-serious adverse events

	Fever	r therapy	C	ontrol					Risk Ratio	Weight
Study	Event	No event	Event	No event					with 95% CI	(%)
Ebel et al.	37	119	17	139				2.1	8 1.28 to 3.70	22.52
Morris et al. A	21	10	9	1	-			0.7	5 0.55 to 1.04	18.03
Morris et al. B	20	10	8	1				0.7	5 0.53 to 1.06	16.30
Morris et al. C	21	10	8	1	-			0.7	6 0.55 to 1.07	16.42
Promes et al.	23	17	15	6	-	÷		0.8	1 0.55 to 1.18	26.06
Tsaganos et al.	2	39	0	39				— 4.7	6 0.24 to 96.16	0.68
Overall								1.1	2 0.91 to 1.37	
Heterogeneity: I <sup>2</sup> =	80.62%	, H <sup>2</sup> = 5.16								
Test of $\theta_i = \theta_i$ : Q(5	) = 25.79	9, p = 0.00								
Test of $\theta = 0$ : $z = 1$	.03, p =	0.30			2010 C					
					1/4 1	4	16	64		
				Favors inte	rvention	Favors co	ntrol	•••		

#### Non-serious adverse events - Fixed-effects meta-analysis

#### Fixed-effects Mantel-Haenszel model

Fixed-effects meta-analysis showed no evidence of a difference between fever control interventions and control interventions on non-serious adverse events (RR 1.12; 95% CI 0.91 to 1.37; p = 0.30;  $I^2 = 80.62$  %; four trials). RR: Risk ratio

CI: Confidence interval

# Figure S23: Subgroup analysis of non-serious adverse events comparing different intervention types

Non-serious adverse events - Subgroup analysis comparing different intervention types											
	Feve	r therapy	С	ontrol					Risk Ratio	Weight	
Study	Event	No event	Event	No event				W	rith 95% CI	(%)	
Ibuprofen											
Morris et al. A	21	10	9	1	-			0.75	0.55 to 1.04	21.70	
Morris et al. B	20	10	8	1	-			0.75	0.53 to 1.06	20.95	
Morris et al. C	21	10	8	1		-		0.76	0.55 to 1.07	21.18	
Promes et al.	23	17	15	6	-			0.81	0.55 to 1.18	19.77	
Heterogeneity: $\tau^2 =$	0.00, l <sup>2</sup> =	= 0.00%, H <sup>2</sup>	= 1.00		•			0.76	0.64 to 0.91		
Test of $\theta_i = \theta_j$ : Q(3)	= 0.09, p	0 = 0.99									
Acetaminophen											
Tsaganos et al.	2	39	0	39		-		- 4.76	0.24 to 96.16	1.01	
Heterogeneity: $\tau^2 =$	0.00, l <sup>2</sup> =	= .%, H <sup>2</sup> = .						4.76	0.24 to 96.16		
Test of $\theta_i = \theta_j$ : Q(0)	= 0.00, p	) = .									
Sulindac											
Ebel et al.	37	119	17	139				2.18	1.28 to 3.70	15.39	
Heterogeneity: $\tau^2 =$	0.00, l <sup>2</sup> =	= .%, H <sup>2</sup> = .				-		2.18	1.28 to 3.70		
Test of $\theta_i = \theta_j$ : Q(0)	= 0.00, p	) = .									
Overall					-			0.92	0.67 to 1.25		
Heterogeneity: $\tau^2 =$	0.09, l <sup>2</sup> =	= 66.50%, H	<sup>2</sup> = 2.98								
Test of $\theta_i = \theta_j$ : Q(5)	= 14.92,	p = 0.01									
Test of group differe	ences: Q	(2) = 14.83	, p = 0.0	0							
<b>.</b> .					1/4 1	4	16 64				
				Favors inter	vention	Favors con	rol				

Non-serious adverse events - Subgroup analysis comparing different intervention types

Random-effects DerSimonian-Laird model

Subgroup analysis comparing different intervention types showed evidence of a subgroup difference (p = 0.00). RR: Risk ratio CI: Confidence interval I<sup>2</sup>: Measure of heterogeneity

### Figure S24: Subgroup analysis of non-serious adverse events comparing critically ill versus non-critically ill

Non-serious adverse events - Subgroup analysis comparing non-critically ill with a combination of critically and non-critically ill

	Feve	r therapy	С	Control				1	<b>Risk Ratio</b>	
Study	Event	No event	Event	No event				W	vith 95% CI	(%)
Non-critically ill										
Ebel et al.	37	119	17	139				2.18	1.28 to 3.70	15.39
Promes et al.	23	17	15	6	-	.,		0.81	0.55 to 1.18	19.77
Tsaganos et al.	2	39	0	39		•		- 4.76	0.24 to 96.16	1.01
Heterogeneity: $\tau^2 = 0.42$ , $I^2 = 79.64\%$ , $H^2$	= 4.91				-			1.44	0.58 to 3.59	
Test of $\theta_i = \theta_j$ : Q(2) = 9.82, p = 0.01										
Both critically and non-critically ill										
Morris et al. A	21	10	9	1				0.75	0.55 to 1.04	21.70
Morris et al. B	20	10	8	1				0.75	0.53 to 1.06	20.95
Morris et al. C	21	10	8	1				0.76	0.55 to 1.07	21.18
Heterogeneity: $\tau^{\scriptscriptstyle 2}$ = 0.00, $I^{\scriptscriptstyle 2}$ = 0.00%, $H^{\scriptscriptstyle 2}$ =	1.00				٠			0.75	0.62 to 0.91	
Test of $\theta_i = \theta_j$ : Q(2) = 0.00, p = 1.00										
Overall					-	•		0.92	0.67 to 1.25	
Heterogeneity: $\tau^2 = 0.09$ , $I^2 = 66.50\%$ , $H^2$	= 2.98									
Test of $\theta_i = \theta_j$ : Q(5) = 14.92, p = 0.01										
Test of group differences: $Q_b(1) = 1.83$ , p	= 0.18									
					1/4 1	4	16 64	+		
				Favors inte	rvention	Favors con	ntrol			

Random-effects DerSimonian-Laird model

Subgroup analysis comparing critically ill with non-critically ill showed no evidence of a subgroup difference (p = 0.18). RR: Risk ratio

CI: Confidence interval

#### Figure S25: Subgroup analysis of non-serious adverse events comparing infectious fever with non-infectious fever

Non-serious adverse events -	Subgro	up analys	sis com	nparing in	fectiou	is fever with no	n-infectio	us fever	
	Fever therapy		Control					Risk Ratio	Weight
Study	Event	No event	Event	No event			W	ith 95% CI	(%)
Infectious fever									
Ebel et al.	37	119	17	139			2.18	1.28 to 3.70	15.39
Tsaganos et al.	2	39	0	39		-	4.76	0.24 to 96.16	1.01
Heterogeneity: $\tau^2 = 0.00$ , $I^2 = 0.00\%$ , $H^2 = 1.00$						-	2.23	1.32 to 3.75	
Test of $\theta_i = \theta_j$ : Q(1) = 0.25, p = 0.62									
Non-infectious fever									
Promes et al.	23	17	15	6		-	0.81	0.55 to 1.18	19.77
Heterogeneity: $\tau^2 = 0.00$ , $I^2 = .\%$ , $H^2 = .$					•		0.81	0.55 to 1.18	
Test of $\theta_i = \theta_j$ : Q(0) = 0.00, p = .									
Unknown if infectious or non-infectious fever					_				
Morris et al. A	21	10	9	1	-		0.75	0.55 to 1.04	21.70
Morris et al. B	20	10	8	1	-		0.75	0.53 to 1.06	20.95
Morris et al. C	21	10	8	1			0.76	0.55 to 1.07	21.18
Heterogeneity: $\tau^2 = 0.00$ , $I^2 = 0.00\%$ , $H^2 = 1.00$					٠		0.75	0.62 to 0.91	
Test of $\theta_i = \theta_j$ : Q(2) = 0.00, p = 1.00									
Overall						•	0.92	0.67 to 1.25	
Heterogeneity: $\tau^2 = 0.09$ , $I^2 = 66.50\%$ , $H^2 = 2.98$									
Test of $\theta_i = \theta_j$ : Q(5) = 14.92, p = 0.01									
Test of group differences: $Q_{b}(2) = 14.67$ , p = 0.00									
				1	/4 1	4 16	64		
				ravors inter	vention	Favors control			

Random-effects DerSimonian-Laird model

Subgroup analysis comparing infectious fever with non-infectious fever showed evidence of a subgroup difference (p = 0.00). RR: Risk ratio CI: Confidence interval

# Figure S26: Subgroup analysis of non-serious adverse events comparing different follow-up times

Non-serious ac	verse	events -	Subgro	oup anal	ysis co	mparing d	ifferent f	ollow	-up times	
	Feve	r therapy	С	ontrol					Risk Ratio	Weight
Study	Event	No event	Event	No event				w	ith 95% CI	(%)
Follow-up time: 1 day										
Tsaganos et al.	2	39	0	39		•		4.76	0.24 to 96.16	1.01
Heterogeneity: $\tau^2 = 0.00$ , $I^2 = .\%$	$H^2 = .$							4.76	0.24 to 96.16	
Test of $\theta_i = \theta_j$ : Q(0) = 0.00, p = .										
Follow-up time: 7 days										
Ebel et al.	37	119	17	139				2.18	1.28 to 3.70	15.39
Heterogeneity: $\tau^2 = 0.00$ , $I^2 = .\%$	$H^2 = .$					-		2.18	1.28 to 3.70	
Test of $\theta_i = \theta_j$ : Q(0) = 0.00, p = .										
Follow-up time: 28 days										
Morris et al. A	21	10	9	1	-			0.75	0.55 to 1.04	21.70
Morris et al. B	20	10	8	1	-			0.75	0.53 to 1.06	20.95
Morris et al. C	21	10	8	1	-			0.76	0.55 to 1.07	21.18
Heterogeneity: $\tau^2 = 0.00$ , $I^2 = 0.00$	00%, H <sup>2</sup> :	= 1.00			٠			0.75	0.62 to 0.91	
Test of $\theta_i = \theta_j$ : Q(2) = 0.00, p = 1	1.00									
Follow-up time: In-hospital										
Promes et al.	23	17	15	6	-	-		0.81	0.55 to 1.18	19.77
Heterogeneity: $\tau^2 = 0.00$ , $I^2 = .%$	$H^2 = .$				-	•		0.81	0.55 to 1.18	
Test of $\theta_i = \theta_j$ : Q(0) = 0.00, p = .										
Overall					•			0.92	0.67 to 1.25	
Heterogeneity: $\tau^2 = 0.09$ , $l^2 = 66$ Test of $\theta_1 = \theta_1$ : Q(5) = 14.92. p =	5.50%, H <sup>a</sup>	<sup>2</sup> = 2.98								
Test of success differences Q (Q)	14.00	- 0.00								
Test of group differences: $Q_b(3)$	= 14.92,	p = 0.00					10 01	-		
				Favors inte	1/4 1 ervention	4 Favors contro	16 64 ol			

Random-effects DerSimonian-Laird model

Subgroup analysis comparing different follow-up times showed evidence of a subgroup difference (p = 0.00). RR: Risk ratio CI: Confidence interval I<sup>2</sup>: Measure of heterogeneity

### Figure S27: Subgroup analysis of non-serious adverse events comparing trials with for profit bias with trials without for-profit bias

for profit bias with trials with no for profit bias											
	Feve	r therapy	С	ontrol				F	Risk Ratio	Weight	
Study	Event	No event	Event	No event				w	ith 95% CI	(%)	
For profit bias											
Tsaganos et al.	2	39	0	39		-		- 4.76	0.24 to 96.16	1.01	
Heterogeneity: $\tau^2 = 0$ .						4.76	0.24 to 96.16				
Test of $\theta_i = \theta_j$ : Q(0) =	0.00, p :	=.									
No for profit bias											
Ebel et al.	37	119	17	139				2.18	1.28 to 3.70	15.39	
Morris et al. A	21	10	9	1	-			0.75	0.55 to 1.04	21.70	
Morris et al. B	20	10	8	1	-			0.75	0.53 to 1.06	20.95	
Morris et al. C	21	10	8	1				0.76	0.55 to 1.07	21.18	
Promes et al.	23	17	15	6	-			0.81	0.55 to 1.18	19.77	
Heterogeneity: $\tau^2 = 0$ .	.09, l² =	70.71%, H <sup>2</sup>	= 3.41		-	e		0.90	0.66 to 1.22		
Test of $\theta_i = \theta_j$ : Q(4) =	13.66, p	0 = 0.01									
Overall								0 92	0.67 to 1.25		
Heterogeneity: $T^2 = 0$	$09 l^2 = 1$	66.50% H <sup>2</sup>	= 2.98					0.02	0.07 10 1.20		
Test of $\theta_i = \theta_j$ : Q(5) =	2.00										
Test of group differen	= 0.28					-					
				1 Favors inter	/4 1 vention	4 Favors co	16 64 ntrol				

Non-serious adverse events - Subgroup analysis comparing trials with

Random-effects DerSimonian-Laird model

Subgroup analysis comparing trials with for profit bias with trials without for profit showed no evidence of a subgroup difference (p = 0.28).

RR: Risk ratio CI: Confidence interval I<sup>2</sup>: Measure of heterogeneity

### Tables

#### Table S1: Characteristics of included trials

Trial ID	Intervention	Control	Number of participant S	Critically ill (Yes/No/B oth)	Infectious fever (Yes/No/U nknown)	All-cause mortality (Interventi on / Control)	Serious adverse events (Interventi on / Control)	Non- serious adverse events (Interventi on / Control)	Quality of life	Temperatu re change p-value*
Azuma et al. A <sup>41</sup>	Zaltoprofen	Placebo	131	No	Yes	N/A	N/A	N/A	N/A	<0.001
Azuma et al. B <sup>41</sup>	Loxoprofen	Placebo	131	No	Yes	N/A	N/A	N/A	N/A	<0.001
Bachert et al. A <sup>42</sup>	Acetylsalicylic acid 500mg	Placebo	97	No	Yes	N/A	N/A	N/A	N/A	<0.001
Bachert et al. B <sup>42</sup>	Acetylsalicylic acid 1000mg	Placebo	97	No	Yes	N/A	N/A	N/A	N/A	<0.001
Bachert et al. C <sup>42</sup>	Acetaminophen 500mg	Placebo	99	No	Yes	N/A	N/A	N/A	N/A	<0.001
Bachert et al. D <sup>42</sup>	Acetaminophen 1000mg	Placebo	99	No	Yes	N/A	N/A	N/A	N/A	<0.001
Bernard et al. <sup>43</sup>	Ibuprofen	Placebo	455	Yes	Yes	70/200 / 74/211	70/200/ 74/211	N/A	N/A	<0.001
DeMartini et al. 44	Physical cooling	No interventio n	16	No	No	N/A	N/A	N/A	N/A	N/A
Diringer et al. <sup>45</sup>	IV-catheter based cooling + standard antipyretic treatment	Standard antipyretic treatment	238	Yes	No	34/123 / 21/115	34/123 / 21/115	N/A	N/A	<0.001
Ebel et al.	Sulindac	Placebo	312	No	Yes	N/A	N/A	37/156 / 17/156	N/A	<0.001
Fankhause r et al. A <sup>46</sup>	Acetylsalicylic acid 1000mg	Placebo	32	No	Unknown	N/A	N/A	N/A	N/A	<0.001
Fankhause r et al. B <sup>46</sup>	Fluproquazone	Placebo	27	No	Unknown	N/A	N/A	N/A	N/A	<0.001
Focan et al. <sup>47</sup>	Suprofen	Placebo	61	Both	Unknown	N/A	N/A	N/A	N/A	<0.05
Gehanno et al. A <sup>48</sup>	6.25mg Diclofenac	Placebo	135	No	Yes	N/A	N/A	N/A	N/A	<=0.05
Gehanno et al. B <sup>48</sup>	12.5mg Diclofenac	Placebo	135	No	Yes	N/A	N/A	N/A	N/A	<0.01
Gehanno et al. C <sup>48</sup>	25mg Diclofenac	Placebo	139	No	Yes	N/A	N/A	N/A	N/A	<0.01
Gehanno et al. D <sup>48</sup>	1000mg Acetaminophen	Placebo	134	No	Yes	N/A	N/A	N/A	N/A	<=0.05
Gozzoli, Schöttker et al. <sup>49</sup>	External cooling	No antipyretic treatment	38	Yes	Unknown	2/18 / 3/20	2/18 / 3/20	N/A	N/A	>0.05

Grebe et al. A <sup>50</sup>	Diclofenac	Placebo	179	No	Yes	N/A	N/A	N/A	N/A	<0.001
Grebe et al. B <sup>50</sup>	Ibuprofen	Placebo	177	No	Yes	N/A	N/A	N/A	N/A	<0.001
Hagobian et al. <sup>51</sup>	Physical cooling	No interventio n	6	No	No	N/A	N/A	N/A	N/A	N/A
Henker et al. A <sup>52</sup>	Antipyretics and physical cooling	Antipyretic s	8	Yes	Unknown	N/A	N/A	N/A	N/A	>0.05
Henker et al. B <sup>52</sup>	Antipyretics and physical cooling	Cooling	9	Yes	Unknown	N/A	N/A	N/A	N/A	>0.05
Honarman d et al. <sup>53</sup>	Intravenous Acetaminophen	No antipyretic treatment	20	Yes	Unknown	2/10 / 3/10	2/10 / 3/10	N/A	N/A	>0.05
Hosokawa et al. <sup>54</sup>	Physical cooling	No interventio n	14	No	No	N/A	N/A	N/A	N/A	N/A
Hosokawa et al. <sup>55</sup>	Physical cooling	No interventio n	14	No	No	N/A	N/A	N/A	N/A	N/A
Kett et al.	Acetaminophen IV	Placebo	60	Both	No	N/A	N/A	N/A	N/A	p=0.0376
Krudsood et al. <sup>57</sup>	IV ibuprofen	Placebo	60	No	Yes	N/A	N/A	N/A	N/A	p=0.0019
Lissoway et al. <sup>58</sup>	Physical cooling	No interventio n	10	No	No	N/A	N/A	N/A	N/A	N/A
Lopez et al. <sup>59</sup>	Cooling vest	Passive cooling	10	No	No	N/A	N/A	N/A	N/A	>0.05
Luhring et al. <sup>60</sup>	Physical cooling	No interventio n	16	No	No	N/A	N/A	N/A	N/A	N/A
Mayer et al. <sup>12</sup>	Acetaminophen + air blanket	Acetamino phen	220	Yes	No	N/A	N/A	N/A	N/A	>0.05
Morgan et al. A <sup>40</sup>	Hypothermia blanket + acetaminophen	Acetamino phen	11	Yes	No	N/A	N/A	N/A	N/A	>0.05
Morgan et al. B <sup>40</sup>	Tepid water sponging + acetaminophen	Acetamino phen	10	Yes	No	N/A	N/A	N/A	N/A	>0.05
Morris et al. A <sup>36</sup>	100 mg IV ibuprofen	Placebo	41	Both	Unknown	1/31 / 1/10	6/31 / 2/10	27/31/ 9/10	N/A	<0.05
Morris et al. B <sup>36</sup>	200mg IV ibuprofen	Placebo	39	Both	Unknown	2/30 / 0/9	5/30 / 1/9	25/30 / 8/9	N/A	<0.05
Morris et al. C <sup>36</sup>	400mg IV ibuprofen	Placebo	40	Both	Unknown	2/31 / 0/9	4/31 / 1/9	23/31 8/9	N/A	<0.001
Mullins et al. A <sup>61</sup>	Acetaminophen + ibuprofen	ibuprofen	38	Yes	No	N/A	N/A	N/A	N/A	>0.05
Mullins et al. B <sup>61</sup>	Acetaminophen + ibuprofen	Acetamino phen	41	Yes	No	N/A	N/A	N/A	N/A	0.03
Niven et al. <sup>62</sup>	Aggressive fever treatment	Permissive fever treatment	26	Yes	Unknown	3/14 / 2/12	3/14 / 2/12	N/A	N/A	0.02
Pernerstor fer et al. A	Aspirin	Placebo	15	No	No	N/A	N/A	N/A	N/A	0.001

Pernerstor fer et al. B	Acetaminophen	Placebo	15	No	No	N/A	N/A	N/A	N/A	0.001
Promes et al. <sup>37</sup>	ibuprofen	Placebo	61	No	No	3/40 / 2/21	6/40 / 6/21	23/40 <i>/</i> 15/21	N/A	<0.05
Salgado et al. A <sup>64</sup>	Ice-packs + antipyretics	Antipyretic s	51	Yes	Unknown	13/34 / 7/17	13/34 / 7/17	N/A	N/A	>0.05
Salgado et al. B <sup>64</sup>	Warm compress + antipyretics	Antipyretic s	51	Yes	Unknown	11/34 / 6/17	11/34 / 6/17	N/A	N/A	>0.05
Schell- Chaple et al. <sup>65</sup>	Acetaminophen	Placebo	40	Yes	Unknown	N/A	N/A	N/A	N/A	0.05
Schortgen, Clabault et al. <sup>66</sup>	External cooling	No external cooling	200	Yes	Yes	43/101 / 48/99	43/101 / 48/99	N/A	N/A	<0.01
Schulman et al. <sup>67</sup>	Aggressive antipyretic protocol	Permissive antipyretic protocol	82	Yes	Unknown	7/44 / 1/38	7/44 / 1/38	N/A	N/A	<0.0001
Schwartz et al. A <sup>68</sup>	Rofecoxib 12.5mg	Placebo	33	No	Unknown	N/A	N/A	N/A	N/A	<0.05
Schwartz et al. B <sup>68</sup>	Rofecoxib 25mg	Placebo	31	No	Unknown	N/A	N/A	N/A	N/A	<0.05
Schwartz et al. C <sup>68</sup>	Ibuprofen 400mg	Placebo	30	No	Unknown	N/A	N/A	N/A	N/A	<0.05
Tan et al.	Physical cooling	No interventio n	22	No	No	N/A	N/A	N/A	N/A	N/A
Tsaganos et al. <sup>38</sup>	Acetaminophen	Placebo	80	No	Yes	2/41 / 0/39	2/41 / 0/39	2/41 / 0/39	N/A	0.003
Vargas et al. A <sup>70</sup>	Keterolac 60mg IM	Placebo IM	40	No	No	N/A	N/A	N/A	N/A	<0.0001
Vargas et al. B <sup>70</sup>	Keterolac 30mg IM	Placebo IM	38	No	No	N/A	N/A	N/A	N/A	<0.0001
Vargas et al. C <sup>70</sup>	Keterolac 15mg IM	Placebo IM	38	No	No	N/A	N/A	N/A	N/A	0.0006
Vargas et al. D <sup>70</sup>	Acetaminophen 650mg PO	Placebo PO	38	No	No	N/A	N/A	N/A	N/A	<0.0001
Vasikasin et al. <sup>71</sup>	Acetaminophen	Placebo	86	No	Yes	0/48 / 0/40	0/48 / 0/40	N/A	N/A	>0.05
Weinkove et al. <sup>35</sup>	Acetaminophen	Placebo	22	No	Yes	0/13 / 2/9	0/13 / 2/9	N/A	Yes	>0.05
Yang et al.	Aggressive antipyretic protocol	Permissive antipyretic protocol	65	Yes	Unknown	21/34 / 8/31	9/22 / 9/32	N/A	N/A	<0.0001
Young P et al. <sup>73</sup>	Acetaminophen	Placebo	690	Yes	Yes	55/346 / 57/344	55/346 / 57/344	N/A	N/A	<0.001
Young P.J. et al. <sup>74</sup>	Aggressive antipyretic protocol	Permissive antipyretic protocol	168	Yes	No	23/89 / 23/89	23/89 / 23/89	N/A	N/A	0.01

Table 2: Characteristics of included trials.

\*p-value for trialist defined temperature difference between fever therapy group and control group. A p-value below or equal to 0.05 represents a significantly lower temperature in the fever therapy group.

		Fever therapy grou	p	Control group			
Trial	Comparison	Number and type of serious adverse event	Proportion of participants with a serious adverse event	Number and type of serious adverse event	Proportion of participants with a serious adverse event		
Bernard et al.	Ibuprofen vs placebo	70 deaths	70/200	70 deaths	74/211		
Diringer et al.	Physical cooling + antipyretics vs antipyretics	34 deaths	34/123	34 deaths	21/115		
Gozzoli, Schöttker et al.	Physical cooling vs no intervention	2 deaths	2/18	3 deaths	3/20		
Honarmand et al.	Acetaminophen vs no intervention	2 deaths	2/10	3 deaths	3/10		
Morris et al. A	Ibuprofen vs placebo	Not stated	6/31	Not stated	2/10		
Morris et al. B	Ibuprofen vs placebo	Not stated	5/30	Not stated	1/9		
Morris et al. C	Ibuprofen vs placebo	Not stated	4/31	Not stated	1/9		
Niven et al.	Acetaminophen + physical cooling vs no intervention	3 deaths	3/14	2 deaths	2/12		
Promes et al.	Ibuprofen vs placebo	1 ARDS, 1 tachypnea, 1 septic shock, 1 septicemia, 1 invasive wound sepsis and 1 breathlessness	6/40	2 ARDs, 1 cardiac arrest, 1 cardiopulmonary arrest, 1 tachypnea and 1 hypotension	6/21		
Salgado et al. A	Physical cooling + antipyretics vs antipyretics	13 deaths	13/34	7 deaths	7/17		
Salgado et al. B	Physical cooling + antipyretics vs antipyretics	11 deaths	11/34	6 deaths	6/17		
Schortgen, Clabault et al.	Physical cooling vs no intervention	43 deaths	43/101	48 deaths	48/99		
Schulman et al.	Acetaminophen + physical cooling vs no intervention	7 deaths	7/44	1 death	1/38		
Tsaganos et al.	Acetaminophen vs placebo	2 deaths	2/41	No serious adverse events	0/39		
Vasikasin et al.	Acetaminophen vs placebo	No serious adverse events	0/48	No serious adverse events	0/40		
Weinkove et al.	Acetaminophen vs	No serious adverse events	0/13	2 deaths	2/7		
Yang et al.	Physical cooling vs no intervention	21 deaths	21/34	8 deaths	8/31		
Young P et al.	Acetaminophen vs placebo	55 deaths	55/346	57 deaths	57/344		
Young P.J. et al.	Acetaminophen vs no intervention	23 deaths	23/89	23 deaths	23/89		

### Table S2: Summary of serious adverse events in the included trials

#### Table S3: Summary of findings table of fever therapy versus control interventions

#### Fever therapy compared with no fever therapy for adults with fever

**Patients or population:** Adults diagnosed with fever of any origin **Setting:** Any setting

**Intervention:** Any type of fever therapy (antipyretics or physical cooling) **Comparison:** No fever therapy (with or without placebo/sham)

Outcome	Anticipated ab (959	osolute effects* % Cl)	Relative effect	No of	Certainty of	Comments	
Outcome	Risk with control	Risk with intervention	(95% CI)	(studies)	(GRADE)		
All-cause mortality Follow-up mean: 25 days	226 per 1,000	<b>235 per 1,000</b> (203 to 269)	<b>RR:</b> 1.04 (0.90 to 1.19)	2415 (16 RCT)	⊕⊕⊕⊕ нісн	-	
Serious adverse events Follow-up mean: 25 days	242 per 1,000	<b>247 per 1,000</b> (215 to 283)	<b>RR:</b> 1.02 (0.89 to 1.17)	2415 (16 RCT)	⊕⊕⊕⊕ HIGH	-	
Non-serious adverse events Follow-up mean: 18 days	234 per 1,000	<b>215 per 1,000</b> (157 to 293)	<b>RR:</b> 0.92 (0.67 to 1.25)	767 (4 RCT)	⊕○○○ VERY LOW <sup>a,b,c</sup>	-	

\*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

RR: Risk ratio CI: Confidence interval; GRADE: GRADE Working Group grades of evidence

**GRADE Working Group grades of evidence** 

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

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

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

#### Explanations

a. Downgraded 2 for risk of bias

b. Downgraded 2 for imprecision due to Trial Sequential Analysis showing no crossing of TSA-monitoring boundaries and insufficient number of participants

c. Downgraded 1 for inconsistency due to large heterogeneity

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