Original Contribution

PAIS 2 (Paracetamol [Acetaminophen] in Stroke 2)
Results of a Randomized, Double-Blind Placebo-Controlled Clinical Trial

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Background and Purpose—Subfebrile body temperature and fever in the first days after stroke are strongly associated with unfavorable outcome. A subgroup analysis of a previous trial suggested that early treatment with paracetamol may improve functional outcome in patients with acute stroke and a body temperature of ≥36.5°C. In the present trial, we aimed to confirm this finding.

Methods—PAIS 2 (Paracetamol [Acetaminophen] in Stroke 2) was a multicenter, randomized, double-blind, placebo-controlled clinical trial. We aimed to include 1500 patients with acute ischemic stroke or intracerebral hemorrhage within 12 hours of symptom onset. Patients were treated with paracetamol in a daily dose of 6 g or matching placebo for 3 consecutive days. The primary outcome was functional outcome at 3 months, assessed with the modified Rankin Scale and analyzed with multivariable ordinal logistic regression. Because of slow recruitment and lack of funding, the study was stopped prematurely.

Results—Between December 2011 and October 2015, we included 256 patients, of whom 136 (53%) were allocated to paracetamol. In this small sample, paracetamol had no effect on functional outcome (adjusted common odds ratio, 1.15; 95% confidence interval, 0.74–1.79). There was no difference in the number of serious adverse events (paracetamol n=35 [26%] versus placebo n=28 [24%]).

Conclusions—Treatment with high-dose paracetamol seemed to be safe. The effect of high-dose paracetamol on functional outcome remains uncertain. Therefore, a large trial of early treatment with high-dose paracetamol is still needed.

Clinical Trial Registration—URL: http://www.trialregister.nl. Unique identifier: NTR2365.
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Key Words: acetaminophen ■ body temperature ■ stroke ■ therapy ■ treatment outcome

High body temperatures after stroke are associated with unfavorable outcome.[1] The risk of poor outcome doubles with every degree Celsius increase in body temperature measured within the first 12 hours from stroke onset.[2]

Animal studies have shown that high body temperature results in increased ischemic damage through increased cerebral metabolic demands, damage of the blood–brain barrier,

acidosis, and an increased release of excitatory amino acids.[3] Lowering body temperature and prevention of fever are, therefore, simple and promising approaches to improve functional outcome after stroke.

There is currently no evidence that strategies to prevent or treat high body temperature reduce case fatality and improve functional outcome after stroke. US stroke guidelines

recommend the use of antipyretic drugs when body temperature exceeds 38.0°C.[4] European Stroke Organisation guidelines do not make any recommendation for treating hyperthermia as a means to improve outcome in patients with ischemic stroke and recommend further research.[5] A possible concern with routine prescription of antipyretic drugs is that this may delay the diagnosis of an infection.

Paracetamol is one of the most commonly prescribed antipyretic drugs. It blocks cerebral cyclooxygenase-2 and lowers cerebral prostaglandin E2 production.[6] In patients with acute stroke, treatment with high-dose paracetamol reduces body temperature by ≈0.3°C within 4 hours after start of treatment.[7] A post hoc analysis of the PAIS trial (Paracetamol [Acetaminophen] in Stroke) suggested that treatment with high-dose paracetamol within 12 hours after stroke onset might improve functional outcome in patients with a body temperature of ≥36.5°C (odds ratio [OR], 1.31; 95% confidence interval [CI], 1.01–1.97).[8,9] The large majority of these patients (n=1.022 [73%]) had a baseline temperature between 36.5°C and 38.0°C and would not have received paracetamol according to the aforementioned guidelines. Although the observed benefit of paracetamol in patients with temperatures >36.5°C is biologically plausible, this should be interpreted with caution because this concerns a subgroup analysis within a randomized clinical trial in which no overall statistically significant benefit could be demonstrated. Confirmation of this observation in an independent study is, therefore, needed.[10] Hence, the aim of PAIS 2 was to assess the effect of high-dose paracetamol on functional outcome in patients with acute stroke and a body temperature of ≥36.5°C in the first 12 hours after stroke onset.

Methods

Study Design and Randomization

PAIS 2 was a multicenter, randomized, double-blind, placebo-controlled clinical trial. The study protocol has been published previously.[9] In short, patients were randomly allocated to treatment with high-dose paracetamol (intervention group) or placebo (control group) in a 1:1 allocation ratio. Treatment allocation was based on a computer-generated list of random numbers with varying block size, linked to a unique treatment number. The list was provided by the independent trial statistician. Local investigators enrolled the patients, and the patients were assigned a box, labeled with a unique study number, containing study medication. Treatment allocation was masked for everyone, except the trial statistician, throughout the trial. The study was approved by a central research ethics committee and the research board of each of the 11 participating centers. All patients or their legal representatives provided written informed consent. The trial was registered in the Netherlands Trial Register (NTR2365) and funded by the Foundation for Neurovascular Research Rotterdam.

Patients

Patients were eligible for inclusion if they had a diagnosis of ischemic stroke or intracerebral hemorrhage, had a body temperature of ≥36.5°C, were ≥18 years, and could be treated within 12 hours after stroke onset. Exclusion criteria were a history of liver disease or alcohol abuse, allergy to paracetamol, liver enzymes (aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, or gamma-glutamyl transpeptidase) increased above twice the upper limit of normal values, death appearing imminent at the time of inclusion, and any prestroke impairment that has led to dependency (modified Rankin Scale [mRS] score >2) and therefore interfering with the assessment of functional outcome.

Procedures

Before inclusion, the diagnosis of ischemic stroke or intracerebral hemorrhage was confirmed by computed tomography or magnetic resonance imaging. Patients were treated with high-dose paracetamol (6 g daily) or matching placebo, started within 12 hours after onset of symptoms and continued for 72 hours or until discharge from hospital if earlier. The study medication (active compound and placebo) was administered through identical tablets or suppositories. In

Table 1.   Baseline Characteristics by Treatment Allocation

	Paracetamol (n=136)	Placebo (n=118)
Medical history		
Age, y (mean, SD)	69 (14)	69 (13)
Male sex	68 (50%)	76 (64%)
Hypertension	78 (57%)	65 (55%)
Atrial fibrillation	15 (11%)	17 (14%)
Diabetes mellitus	20 (15%)	20 (17%)
Previous stroke	33 (24%)	22 (19%)
Smoking	61 (45%)	55 (47%)
Pre-mRS score (median, IQR)	0 (0–0)	0 (0–0)
Physical examination		
NIHSS at admission (median, IQR)	6 (3–8)	5 (2–8)
Systolic blood pressure at admission, mm Hg (median, IQR)	154 (140–170)	160 (144–170)
Diastolic blood pressure at admission, mm Hg (median, IQR)	81 (70–90)	82 (70–90)
Heart rate at admission, bpm (median, IQR)	79 (69–89)	79 (70–89)
Body temperature at admission, °C (median, IQR)	36.9 (36.7–37.2)	36.8 (36.6–37.2)
CRP at admission, mg/L (median, IQR)	3 (1–8)	3 (1–7)
Stroke type		
Ischemic stroke	127 (93%)	107 (91%)
Ischemic stroke subtype*		
Large vessel disease	22 (17%)	19 (18%)
Cardiac embolism	21 (17%)	16 (15%)
Small vessel disease	26 (20%)	21 (20%)
Other	6 (5%)	11 (10%)
Unknown	52 (41%)	40 (37%)
Treatment characteristics		
Treatment with r-tPA	63 (47%)	53 (45%)
Time from onset to randomization, min (median, IQR)	363 (243–570)	390 (270–600)
Treatment with study medication within 6 h after onset of symptoms	68 (50%)	63 (53%)

CRP indicates C-reactive protein; IQR, interquartile range; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; r-tPA, recombinant tissue-type plasminogen activator; and SD, standard deviation.

*Based on the definitions of the Trial of ORG 10172 in Acute Stroke Therapy (TOAST) criteria.
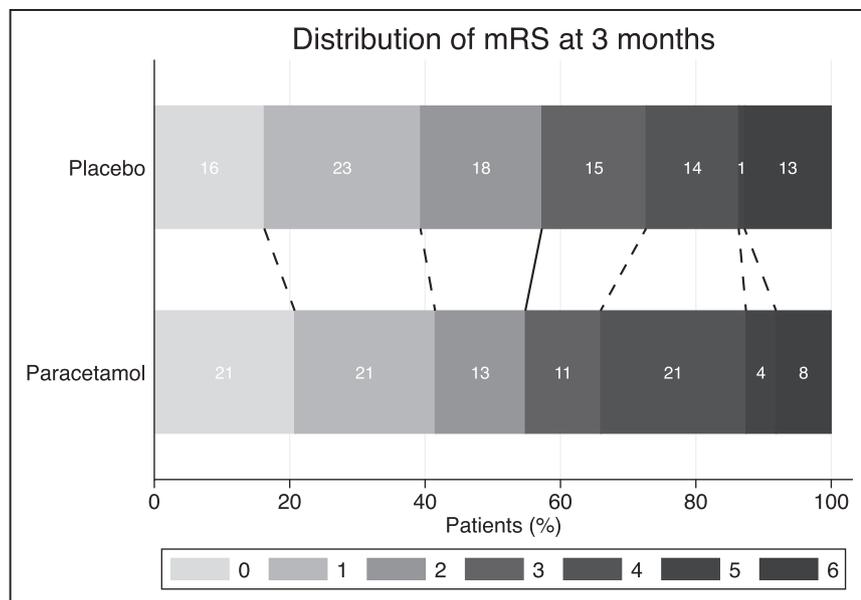
Figure 1. Distribution of the scores on the modified Rankin Scale (mRS) at 90 days.

the first 3 days of enrollment, concurrent treatment with open-label paracetamol was not allowed. The use of other antipyretic medication was allowed. Baseline characteristics were collected, and at 3 months, outcome scores and (serious) adverse events, including infections, were assessed by telephone interview by experienced research nurses of the trial office of the neurovascular division of the Erasmus MC University Medical Center Rotterdam. For more details, we refer to the study protocol.[9]

Outcome

The primary outcome was the shift on the mRS score at 90 days.[11] Secondary outcomes were body temperature at 24 hours after start of treatment, unfavorable outcome at 90 days, defined as a score on the mRS of ≥3, activities of daily life, measured with the Barthel Index,[12] and quality of life, measured with the EuroQol 5D 3L score at 90 days, estimated with the Dutch tariff.[13]

Sample Size

We assumed an effect of paracetamol that leads to a 7% absolute increase in the cumulative proportion of patients with mRS score between 0 and 2 in the paracetamol group, compared with that of

the placebo. We used a power (1-beta) of 0.85 to detect a significant difference in the scores on the mRS of the paracetamol group compared with the placebo group at a level of significance of 0.05. The total study size needed was calculated and rounded to 1500 patients.

Statistical Analysis

Statistical analyses were performed according to the intention-to-treat principle. The primary effect estimate was the common OR of improvement on the mRS score assessed by means of multiple ordinal logistic regression analysis. A common OR >1 would indicate a positive effect of treatment, with shift toward better functional outcome. Adjustments were made for age, National Institutes of Health Stroke Scale at admission, and stroke type. For the continuous variables EuroQol 5D 3L and body temperature difference, we used linear regression analysis. We tested for heterogeneity of treatment effect across important clinical subgroups of patients, as defined in the study protocol.[9] We also performed a systemic review of literature and updated a previous meta-analysis of paracetamol in acute stroke, both for all patients and for patients with a body temperature of ≥36.5°C (when data available).[8] Data were added to the meta-analysis at individual patient level. Favorable outcome in

Table 2.   Clinical and Safety Outcomes and Treatment Effects

	Paracetamol (n=135)	Placebo (n=117)	Effect Variable	Unadjusted Value (95% CI)	Adjusted Value (95% CI)
Primary outcome					
mRS at 90 days (median, IQR)	2 (1–4)	2(1–4)	Common odds ratio	1.02 (0.66 to 1.58)	1.15 (0.74 to 1.79)
Secondary outcomes					
Favorable outcome at 90 days (mRS 0–2)	74 (54%)	67 (57%)	Odds ratio	0.91 (0.67 to 1.81)	1.01 (0.55 to 1.78)
Barthel index at 90 days (BI=100)	71 (52%)	64 (54%)	Odds ratio	0.92 (0.56 to 1.51)	1.02 (0.58 to 1.80)
EQ-5D at 90 days (median, IQR)	7 (5–9)	7 (5–9)	Beta	0.15 (−0.49 to 0.78)	−0.16 (−0.72 to 0.40)
Body temperature at 24 h, °C (median, IQR)	36.8 (36.7–37.3)	37.0 (36.7–37.3)	Beta	−0.22 (−0.37 to −0.06)	−0.25 (−0.40 to −0.11)
Body temperature difference baseline–24 h (mean, SD)	−0.09 (0.61)	0.18 (0.62)	Beta	−0.27 (−0.44 to −0.11)	−0.26 (−0.40 to −0.12)

Adjustment were made for age, NIHSS at admission, and stroke type. CI indicates confidence interval; EQ-5D, EuroQol 5D; IQR, interquartile range; mRS, modified Rankin Scale; and NIHSS, National Institutes of Health Stroke Scale.

Table 3. Safety Outcomes

	Paracetamol (n=135)	Placebo (n=117)
Safety variables		
Death within 7 days	5 (4%)	7 (6%)
Death within 90 days	11 (8%)	15 (13%)
Serious adverse events		
Any serious adverse event	35 (26%)	28 (24%)
Pneumonia	4 (3%)	3 (3%)
Urinary tract infection	3 (2%)	3 (2%)
Other infection	0 (0%)	1 (1%)
Liver failure	0 (0%)	0 (0%)
Gastrointestinal hemorrhage	1 (1%)	0 (0%)

this meta-analysis was defined as an mRS score 0 to 2. The effect estimate was OR, with an OR >1 indicating a positive effect of treatment. All analyses were performed with STATA 14 (StataCorp. 2015. Stata Statistical Software: Release 14; StataCorp LP, College Station, TX).

Results

Baseline Characteristics

Recruitment started in December 2011, and inclusion was halted on October 1, 2014, because of slow recruitment and lack of funding. The trial ended on January 1, 2015. In total, 256 patients were randomized, of whom 136 (53%) were allocated to paracetamol (Figure I in the online-only Data Supplement). Two patients withdrew informed consent. Mean age was 69 years in both groups. Baseline characteristics did not differ between the treatment groups, except for sex (paracetamol 50% men; placebo 64% men; Table 1). Two patients (0.4%) were lost to follow-up.

Clinical Outcomes

We found no difference in improvement on the mRS score between patients treated with paracetamol and those treated with placebo (common OR, 1.02; 95% CI, 0.66–1.58; Figure 1). Adjustment for age, National Institutes of Health Stroke Scale at admission, and stroke type had no appreciable effect (adjusted common OR, 1.15; (95% CI, 0.74–1.79). The treatment had no effect on secondary outcome measures (Table 2), except for body temperature at 24 hours, which was significantly lower in paracetamol-treated patients compared with that of control patients (median body temperature at 24 hours in paracetamol-treated patients 36.8°C versus 37.0°C in placebo-treated patients; mean temperature difference −0.27°C; 95% CI, −0.44°C to −0.11°C). We did not find a statistically significant effect of paracetamol on functional outcome in any prespecified subgroup (Figure II in the online-only Data Supplement).

Safety Outcomes

Mortality at 3 months did not differ between the paracetamol and placebo groups (n=11 [8%] versus n=15 [13%],
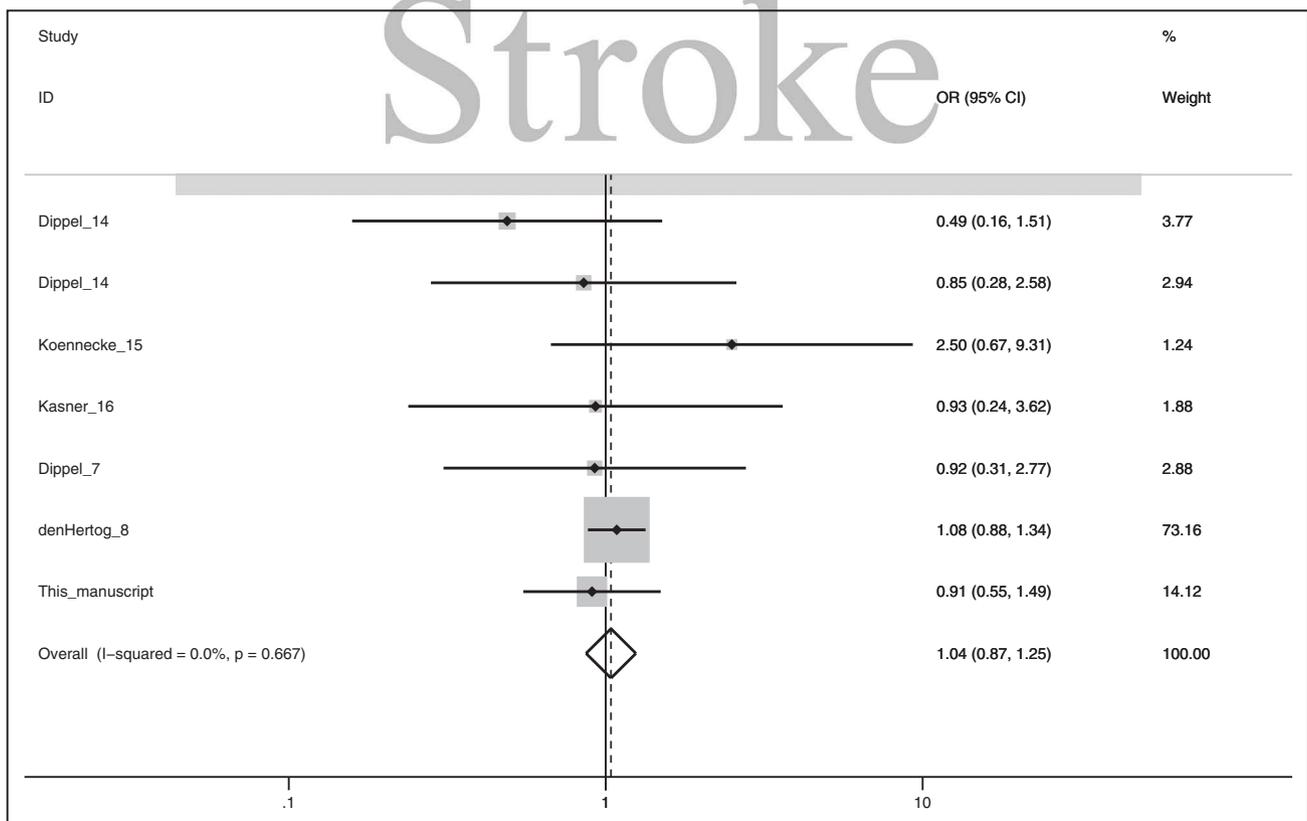

Figure 2. Updated meta-analysis of all studies with paracetamol after acute stroke. Favorable outcome is defined as a modified Rankin Scale (mRS) score 0 to 2. An odds ratio (OR) >1 indicates a positive effect of treatment. CI indicates confidence interval.

respectively). There were no cases of liver failure, and the rate of infections was similar in both groups (Table 3).

Meta-Analysis

The overall OR in the meta-analysis of all controlled trials with paracetamol after acute stroke did not indicate a difference between paracetamol and placebo (OR, 1.04; 95% CI, 0.87–1.25; Figure 2).[7,8,14–16] Figure III in the online-only Data Supplement shows the meta-analysis of data from patients with a baseline temperature of ≥36.5°C, with similar results (overall OR, 1.08; 95% CI, 0.88–1.33).

Discussion

In this prematurely terminated small trial in patients with acute stroke and a body temperature of ≥36.5°C, we found that treatment with high-dose paracetamol was safe, but did not improve functional outcome at 3 months. Treatment with paracetamol lowered body temperature by 0.3°C.

Therapeutic hypothermia has been accepted as an effective treatment after cardiac arrest[17] and in hypoxic–ischemic encephalopathy in neonates.[18] An important issue in the ongoing discussion on cardiac arrest is the optimal target temperature. A recent study showed that a target temperature of 36.0°C may be noninferior to therapeutic hypothermia aiming at a body temperature of 33.0°C to 34.0°C.[19] In that study, patients who were maintained at a target of 36.0°C seemed to have less serious side effects, including hypokalemia, pneumonia, and bleeding complications, but these differences were not statistically significant, except for hypokalemia ($P=0.02$).[19] Other subjects of debate are time to initiation of hypothermia, time to achieve target temperature, treatment duration, and rewarming methods.[20] These issues are also applicable to therapeutic hypothermia in acute stroke.[21]

Although clinical studies assessing the effect of therapeutic hypothermia on outcome after acute stroke have to date been too small to demonstrate a benefit, pharmacological treatment aimed at maintaining normothermia may be an alternative. Six studies have been performed on pharmacological hypothermia in acute stroke. Five of these studies used paracetamol as antipyretic drug.[22] These studies, except for PAIS, were small and designed to test safety and feasibility. They showed no effect on outcome. In PAIS, more patients in the paracetamol group than in the placebo group improved beyond expectation, but this effect was just not statistically significant (adjusted OR, 1.20; 95% CI, 0.96–1.50). In a post hoc analysis of a subgroup of patients with a body temperature of ≥37.0°C, treatment with paracetamol was associated with improved outcome. A previous meta-analysis using a dichotomized outcome showed a trend toward a favorable effect of temperature-lowering treatment.[22] Furthermore, the QASC trial (Quality in Acute Stroke Care) showed that early detection and management of fever (body temperature >37.5°C), swallowing difficulties, and hyperglycemia led to a significantly higher chance of being alive or independent during follow-up.[23] This trial was, however, not designed to determine which of these interventions made the difference.

The results of PAIS 2 are neutral. However, because of serious lack of power, we cannot exclude an alternative result. We updated the previous meta-analysis with the results of PAIS 2 (Figure 2) and found no significant difference between temperature-lowering treatment and control in the proportion of patients who were alive and independent (mRS score ≤2; overall OR, 1.04; 95% CI, 0.87–1.25). We also performed a meta-analysis of data of all patients with a baseline temperature of ≥36.5°C (Figure III in the online-only Data Supplement), which showed comparable results (overall OR, 1.08; 95% CI, 0.88–1.33). However, these analyses were binary and did not have the advantage of ordinal regression analysis.

The main limitation of this study is that it was preliminarily stopped, and therefore, the study is strongly underpowered to detect a difference in functional outcome after treatment with high-dose paracetamol in acute stroke. Patient recruitment was low, which was most likely caused by the low intensity of trial coordination activities, such as creating awareness for the study and providing information, feedback, and support to the participating centers. This was a consequence of the low budget. The simultaneous conduct of several large randomized clinical trials of acute stroke treatment in The Netherlands also added to the low recruitment rate. A strength of the study is that it allowed us to update the meta-analysis with the results of this study.

The results of PAIS 2 provide no evidence for the routine use of high-dose paracetamol in acute stroke. Although the relative effect may be low, an absolute risk reduction in unfavorable outcome of 5% may be clinically relevant, considering the large number of patients involved and the simple, safe, and cheap nature of the therapy. Taking into account the results of the updated meta-analysis, such a moderate effect could not be excluded. Further large clinical trials are necessary to further explore this finding. This will be assessed in the PRECIOUS trial (Prevention of Complications to Improve Outcome in Elderly Patients With Stroke; www.precious-trial.eu).

Conclusions

Treatment with paracetamol after acute stroke seems to be safe. However, the effect of treatment with high-dose paracetamol after acute stroke remains unclear. A large trial of early treatment with paracetamol after acute stroke is needed to answer this question.

Appendix

Trial Organization

Executive Committee
D.W.J. Dippel, H.B. van der Worp, and I.R. de Ridder

Steering Committee
D.W.J. Dippel (principal investigator), H.B. van der Worp (principal investigator), I.R. de Ridder (trial coordinator), H.F. Lingsma (trial statistician), H.M. den Hertog, H.M.A. van Gemert, A.H.C.M.L. Schreuder, A. Ruitenberg, R. Saxena, E. Maasland, J.H. van Tuijl, B.P.W. Jansen, R.M. Van den Berg-Vos, F. Vermeij, P.J. Koudstaal, L.J. Kappelle, and A. Algra

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N. El Ghannouti

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H.B. van der Worp (University Medical Center Utrecht, Utrecht; 42 patients)

D.W.J. Dippel (Erasmus MC University Medical Center, Rotterdam; 40 patients)

A.H.C.M.L. Schreuder (Zuyderland Medical Center, Heerlen; 36 patients)

H.M. den Hertog (Medical Spectrum Twente, Enschede; 15 patients)
J.H. van Tuijl and B.P.W. Jansen (Elisabeth Twee Steden Hospital; 14 patients)
E. Maasland (Van Weel-Bethesda Hospital, Dirksland; 11 patients)
R.M. Van den Berg-Vos (OLVG location West, Amsterdam; 8 patients)
R. Saxena (Maasstad Hospital, Rotterdam; 4 patients)
A. Ruitenberg (Admiraal de Ruyter Hospital, Goes; 4 patients)
F. Vermey (Franciscus Gasthuis, Rotterdam; 2 patients)

Data Monitoring and Safety Committee
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References

1. Azzimondi G, Bassein L, Nonino F, Fiorani L, Vignatelli L, Re G, et al. Fever in acute stroke worsens prognosis. A prospective study. *Stroke*. 1995;26:2040–2043.
2. Reith J, Jørgensen HS, Pedersen PM, Nakayama H, Raaschou HO, Jeppesen LL, et al. Body temperature in acute stroke: relation to stroke severity, infarct size, mortality, and outcome. *Lancet*. 1996;347:422–425.
3. Ginsberg MD, Busto R. Combating hyperthermia in acute stroke: a significant clinical concern. *Stroke*. 1998;29:529–534.
4. Jauch EC, Saver JL, Adams HP Jr, Bruno A, Connors JJ, Demaerschalk BM, et al; American Heart Association Stroke Council; Council on Cardiovascular Nursing; Council on Peripheral Vascular Disease; Council on Clinical Cardiology. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2013;44:870–947. doi: 10.1161/STR.0b013e318284056a.
5. European Stroke Organisation (ESO) Executive Committee, ESO Writing Committee. Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. *Cerebrovasc Dis*. 2008;25:457–507. doi: 10.1159/000131083.
6. Kis B, Snipes JA, Simandle SA, Busija DW. Acetaminophen-sensitive prostaglandin production in rat cerebral endothelial cells. *Am J Physiol Regul Integr Comp Physiol*. 2005;288:R897–R902. doi: 10.1152/ajpregu.00613.2004.
7. Dippel DW, van Breda EJ, van der Worp HB, van Gemert HM, Meijer RJ, Kappelle LJ, et al; PISA-Investigators. Effect of paracetamol (acetaminophen) and ibuprofen on body temperature in acute ischemic stroke PISA, a phase II double-blind, randomized, placebo-controlled trial [ISRCTN98608690]. *BMC Cardiovasc Disord*. 2003;3:2. doi: 10.1186/1471-2261-3-2.
8. den Hertog HM, van der Worp HB, van Gemert HM, Algra A, Kappelle LJ, van Gijn J, et al; PAIS Investigators. The Paracetamol (Acetaminophen) In Stroke (PAIS) trial: a multicentre, randomised, placebo-controlled, phase III trial. *Lancet Neurol*. 2009;8:434–440. doi: 10.1016/S1474-4422(09)70051-1.
9. de Ridder IR, de Jong FJ, den Hertog HM, Lingsma HF, van Gemert HM, Schreuder AH, et al. Paracetamol (Acetaminophen) in stroke 2 (PAIS 2): protocol for a randomized, placebo-controlled, double-blind clinical trial to assess the effect of high-dose paracetamol on functional outcome in patients with acute stroke and a body temperature of 36.5°C or above. *Int J Stroke*. 2015;10:457–462. doi: 10.1111/ijs.12053.
10. den Hertog HM, van der Worp HB, van Gemert HM, Algra A, Kappelle LJ, van Gijn J, et al; PAIS investigators. High-dose paracetamol in stroke: new trials are necessary and feasible. *Lancet Neurol*. 2009;8:700–701; author reply 701. doi: 10.1016/S1474-4422(09)70191-7.
11. van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke*. 1988;19:604–607.
12. Mahoney FI, Barthel DW. Functional evaluation: the Barthel index. *Md State Med J*. 1965;14:61–65.
13. Versteegh M, Vermeulen K, Evers S, de Wit GA, Prenger R, A. Stolk E. Dutch tariff for the five-level version of EQ-5D. *Value Health*. 2016;19:343–352. doi: 10.1016/j.jval.2016.01.003.
14. Dippel DW, van Breda EJ, van Gemert HM, van der Worp HB, Meijer RJ, Kappelle LJ, et al. Effect of paracetamol (acetaminophen) on body temperature in acute ischemic stroke: a double-blind, randomized phase II clinical trial. *Stroke*. 2001;32:1607–1612.
15. Koennecke HC, Leistner S. Prophylactic antipyretic treatment with acetaminophen in acute ischemic stroke: a pilot study. *Neurology*. 2001;57:2301–2303.
16. Kasner SE, Wein T, Piriyawat P, Villar-Cordova CE, Chalela JA, Krieger DW, et al. Acetaminophen for altering body temperature in acute stroke: a randomized clinical trial. *Stroke*. 2002;33:130–134.
17. Bernard SA, Gray TW, Buist MD, Jones BM, Silvester W, Gutteridge G, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med*. 2002;346:557–563. doi: 10.1056/NEJMoa003289.
18. Shankaran S, Laptook AR, Ehrenkranz RA, Tyson JE, McDonald SA, Donovan EF, et al; National Institute of Child Health and Human Development Neonatal Research Network. Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy. *N Engl J Med*. 2005;353:1574–1584. doi: 10.1056/NEJMcps050929.
19. Nielsen N, Wetterslev J, Cronberg T, Erlinge D, Gasche Y, Hassager C, et al; TTM Trial Investigators. Targeted temperature management at 33°C versus 36°C after cardiac arrest. *N Engl J Med*. 2013;369:2197–2206. doi: 10.1056/NEJMoa1310519.
20. Fukuda T. Targeted temperature management for adult out-of-hospital cardiac arrest: current concepts and clinical applications. *J Intensive Care*. 2016;4:30. doi: 10.1186/s40560-016-0139-2.
21. van der Worp HB, Macleod MR, Kollmar R; European Stroke Research Network for Hypothermia (EuroHYP). Therapeutic hypothermia for acute ischemic stroke: ready to start large randomized trials? *J Cereb Blood Flow Metab*. 2010;30:1079–1093. doi: 10.1038/jcbfm.2010.44.
22. Den Hertog HM, van der Worp HB, Tseng MC, Dippel DW. Cooling therapy for acute stroke. *Cochrane Database Syst Rev*. 2009:CD001247. doi: 10.1002/14651858.CD001247.pub2.
23. Middleton S, McElduff P, Ward J, Grimshaw JM, Dale S, D'Este C, et al; QASC Trialists Group. Implementation of evidence-based treatment protocols to manage fever, hyperglycaemia, and swallowing dysfunction in acute stroke (QASC): a cluster randomised controlled trial. *Lancet*. 2011;378:1699–1706. doi: 10.1016/S0140-6736(11)61485-2.

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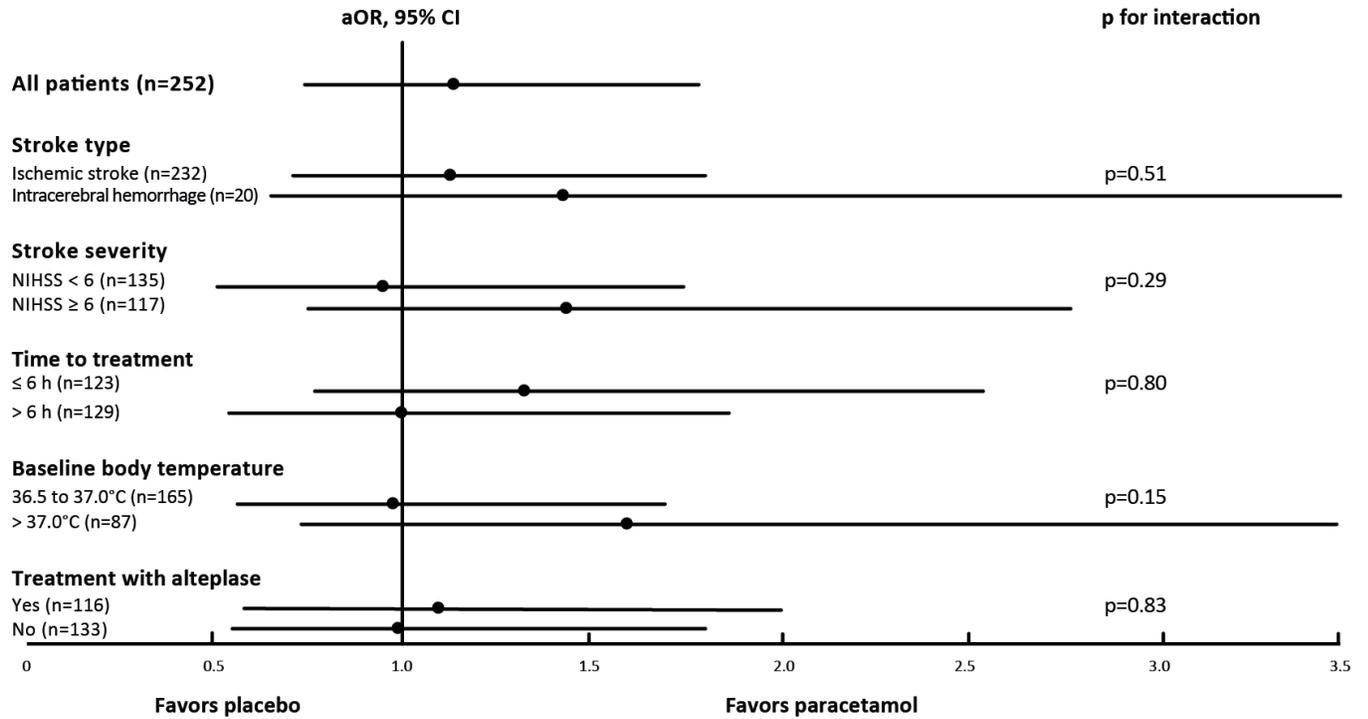
SUPPLEMENTAL MATERIAL
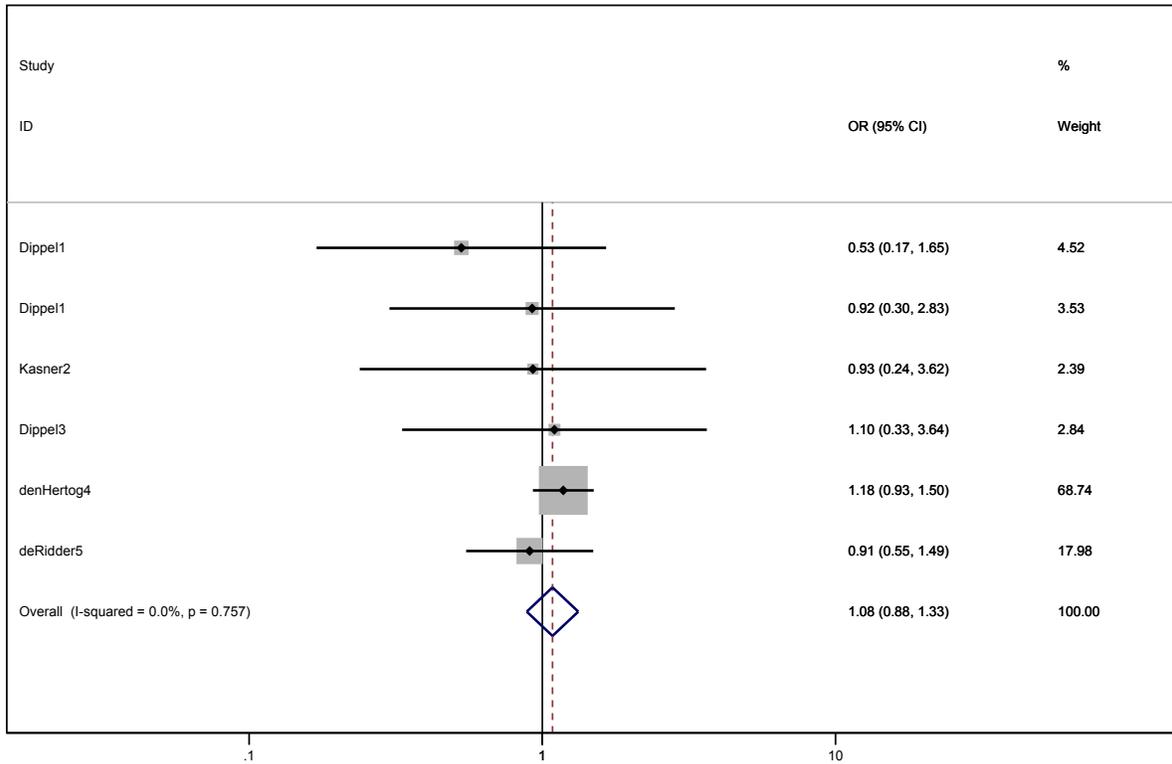
Supplemental Figure I

CONSORT 2010 Flow Diagram.
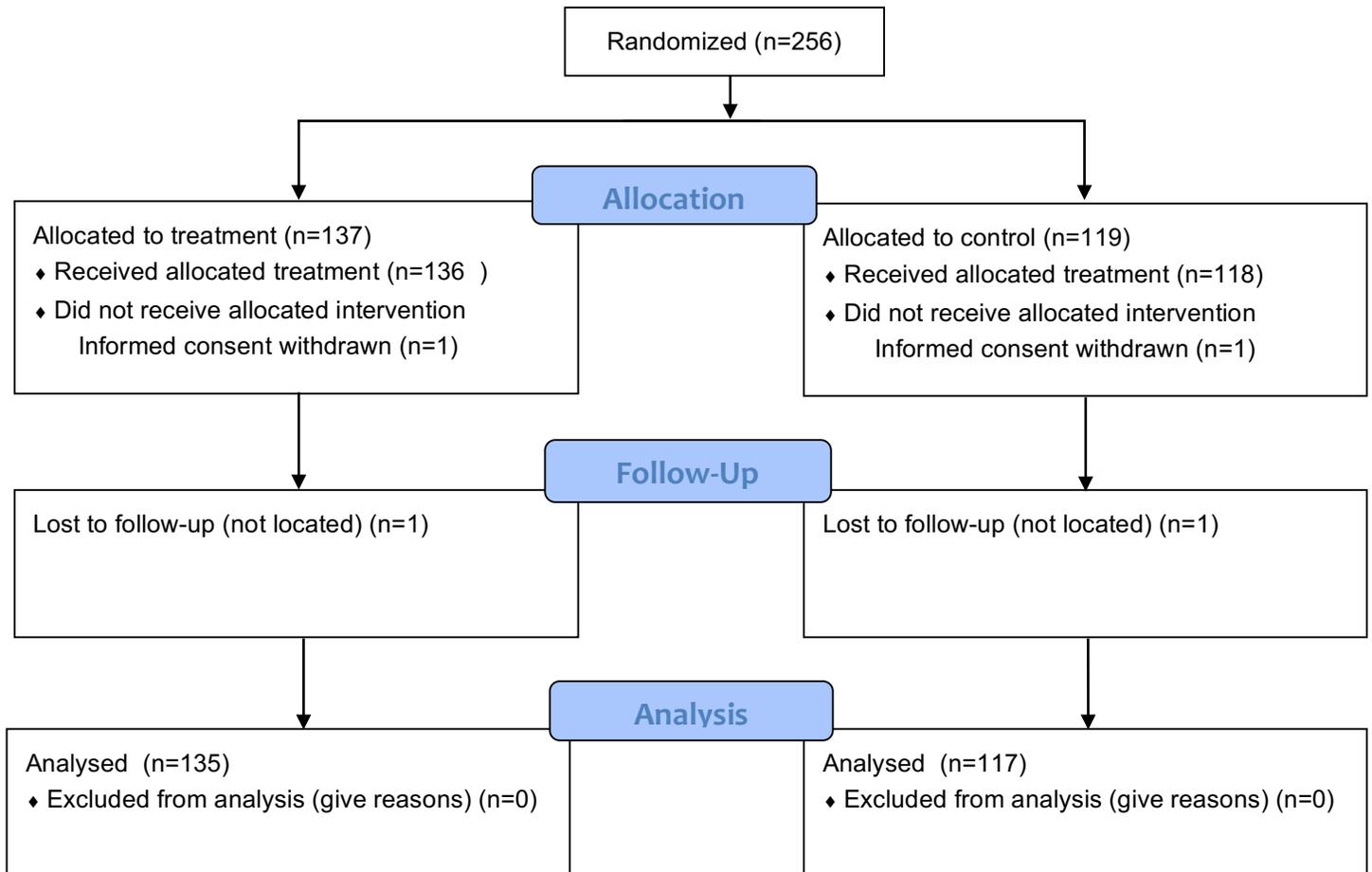
Supplemental Figure II

Subgroup Analysis. Adjusted Odds Ratio (aOR; black dots), 95% Confidence Interval (Cis; horizontal lines), P values for the interaction between the treatment effect and any subgroup variable.

Supplemental Figure III

Updated meta-analysis of all studies with paracetamol after acute stroke in patients with a body temperature of 36.5 degrees and higher. Favorable outcome is defined as an mRS 0-2. An OR larger than 1 indicates a positive effect of treatment.

Study ID	OR (95% CI)	% Weight
Dippel1	0.53 (0.17, 1.65)	4.52
Dippel1	0.92 (0.30, 2.83)	3.53
Kasner2	0.93 (0.24, 3.62)	2.39
Dippel3	1.10 (0.33, 3.64)	2.84
denHertog4	1.18 (0.93, 1.50)	68.74
deRidder5	0.91 (0.55, 1.49)	17.98
Overall (I-squared = 0.0%, p = 0.757)	1.08 (0.88, 1.33)	100.00

References

1. Dippel DW, van Breda EJ, van Gemert HM, van der Worp HB, Meijer RJ, Kappelle LJ, et al. Effect of paracetamol (acetaminophen) on body temperature in acute ischemic stroke: A double-blind, randomized phase ii clinical trial. *Stroke*. 2001;32:1607-1612
2. Kasner SE, Wein T, Piriyawat P, Villar-Cordova CE, Chalela JA, Krieger DW, et al. Acetaminophen for altering body temperature in acute stroke: A randomized clinical trial. *Stroke*. 2002;33:130-134
3. Dippel DW, van Breda EJ, van der Worp HB, van Gemert HM, Meijer RJ, Kappelle LJ, et al. Effect of paracetamol (acetaminophen) and ibuprofen on body temperature in acute ischemic stroke pisa, a phase ii double-blind, randomized, placebo-controlled trial [isrctn98608690]. *BMC Cardiovasc Disord*. 2003;3:2
4. den Hertog HM, van der Worp HB, van Gemert HM, Algra A, Kappelle LJ, van Gijn J, et al. The paracetamol (acetaminophen) in stroke (pais) trial: A multicentre, randomised, placebo-controlled, phase iii trial. *Lancet Neurol*. 2009;8:434-440

5. This manuscript