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Intravascular Versus Surface Cooling in Patients Resuscitated From Cardiac Arrest: A Systematic Review and Network Meta-Analysis With Focus on Temperature Feedback

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OBJECTIVE: The aim of the study was to compare the effect of intravascular cooling (IC), surface cooling with temperature feedback (SCF), and surface cooling without temperature feedback (SCnoF) on neurologic outcome and survival in patients successfully resuscitated from cardiac arrest (CA) and treated with targeted temperature management (TTM) at 32–34°C.

DATA SOURCES: We performed a systematic review on Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, MEDLINE, SCOPUS, CINAHL, Web of Science, and Clinical Trials up to June 30, 2021.

STUDY SELECTION: We included randomized and nonrandomized studies on IC, SCF, and SCnoF in adult humans resuscitated from CA undergoing TTM, reporting neurologic outcome or survival.

DATA EXTRACTION: We performed a network meta-analysis to assess the comparative effects of IC, SCF, and SCnoF. The overall effect between two cooling methods included the effect of direct and indirect comparisons. Results are given as odds ratios (OR) and 95% CIs. Rankograms estimated the probability of TTM methods being ranked first, second, and third best interventions.

DATA SYNTHESIS: A total of 14 studies involving 4,062 patients met the inclusion criteria. Four studies were randomized controlled studies, and 10 studies were nonrandomized observational studies. IC compared with SCnoF was significantly associated with better neurologic outcome (OR, 0.6; 95% CI, 0.49–0.74) and survival (OR, 0.8; 95% CI, 0.66–0.96). IC compared with SCF, and SCF compared with SCnoF did not show significant differences in neurologic outcome and survival. The rankogram showed that IC had the highest probability to be the most beneficial cooling method, followed by SCF and SCnoF.

CONCLUSIONS: Our results suggest that in patients resuscitated from CA and treated with TTM at 32–34°C, IC has the highest probability of being the most beneficial cooling method for survival and neurologic outcome.

KEY WORDS: cardiac arrest; cooling; network meta-analysis; neurologic outcome; survival; targeted temperature management

Targeted temperature management (TTM) is recommended in unconscious survivors resuscitated from cardiac arrest (CA) with a recommended temperature range between 32°C and 36°C (1). However, the recently published Targeted Hypothermia versus Targeted Normothermia after Out-of-Hospital Cardiac Arrest (TTM2) trial (2), showing no difference in outcome between TTM at 33°C and TTM at 37.5°C in postresuscitation care, might challenge these recommendations, and another controversy

DOI: 10.1097/CCM.0000000000005463

is foreseeable. TTM can be induced and maintained by various methods, including invasive cooling methods (intravascular cooling) and noninvasive cooling methods (surface cooling) (3). Although intravascular cooling devices operate with automated temperature feedback, surface cooling devices operate either with or without temperature feedback (3). The optimal cooling method for TTM remains a matter of debate. Recently, four meta-analyses have been conducted in attempt to elucidate this issue (4–7). The main limitation of these meta-analyses is the fact that the authors did not differentiate whether surface cooling was applied with or without temperature feedback. This differentiation is of great importance, since several studies have shown that cooling without feedback devices results in significant fluctuations in body temperature (8–10), which per se is associated with poor neurologic outcome (11). It remains unclear, if invasive cooling is superior to surface cooling, when surface cooling includes temperature feedback.

The aim of this network meta-analysis was to compare the effect of invasive cooling, surface cooling with temperature feedback, and surface cooling without temperature feedback on neurologic outcome and survival in patients successfully resuscitated from CA and treated with TTM at 32–34°C.

MATERIALS AND METHODS

Reporting Guidelines and Protocol Registration

We followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocols guidelines (12). The review protocol was registered with International Prospective Register of Systematic Reviews (PROSPERO) on January 27, 2020, and finally approved on April 28, 2020 (CRD42020166910) at http://www.crd.york.ac.uk/PROSPERO/.

Data Sources and Search Strategies

We searched the following databases: The Cochrane Library Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews, MEDLINE, SCOPUS, CINAHL, Web of Science, and ClinicalTrials.gov up to June 30, 2021. We checked citations of screened studies and reviews for relevant articles and searched clinical trial databases like World Health Organization International Clinical Trials Registry Platform and clinicaltrials.gov for any unpublished data.

We built a BOOLEAN search strategy (**Appendix**, http://links.lww.com/CCM/H5) without any restrictions to publication date, study design, or language, and exported it to the reference management software (Endnote Version x9; Clarivate Analytics, London, United Kingdom).

Study Screening and Selection

Two independent reviewers (N.R., R.K.) selected articles by titles and abstracts. The full text of the selected articles was scanned for inclusion by the consensus between the two reviewers (N.R., R.K.). In divergent cases, a third reviewer (W.B.) was involved to make a decision.

Inclusion Criteria

Types of Studies.

- Randomized studies (including quasi-randomized studies and cluster-randomized studies)
- Nonrandomized controlled studies (including controlled before-and-after studies, interrupted time series studies, and historically controlled studies).

Types of Participants.

- Human and adult (either defined as “18 years or older” or not specified) participants resuscitated from CA undergoing TTM.

Types of Interventions.

- Intravascular cooling (with temperature feedback-mechanisms)
- Surface cooling methods with temperature feedback-mechanisms
- Surface cooling methods without temperature feedback-mechanisms

Types of Outcome Measures.

- Neurologic outcome
- Survival

Outcome Parameter

The primary outcome was good neurologic outcome in terms of cerebral performance categories of 1 and 2, or modified Rankin Scale of 3 or less. The secondary outcome was survival. The included studies reported various time points for outcome assessment, ranging from hospital stay up to 6 months. If a study reported more than one time point for outcome evaluation, we choose the longest observation period for the respective study (13).

Statistical Analysis

Data Extraction and Analysis. Data extraction was performed by two reviewers (N.R., R.K.). In the cases of disagreement, the third reviewer (W.B.) was involved to make a decision. We extracted all relevant data into an electronic data extraction form and Cochrane Review Manager Version 5.3 (Cochrane, London, United Kingdom). In case that randomized controlled trials (RCTs) provided different information on intention to treat (ITT) and per protocol analysis, we used the numbers from the ITT analysis for our outcome parameters.

Risk of Bias and Level of Evidence. We assessed included RCTs using the Version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2) tool (14) and nonrandomized studies using Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool (15). The level of evidence was rated in accordance with guidelines of the Centre for Evidence-Based Medicine (16).

Network Meta-Analysis. An NMA was performed to simultaneously assess the comparative effects of the three interventions: intravascular cooling, surface cooling with temperature feedback, and surface cooling without temperature feedback. We used the PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-analyses of Health Care Interventions as basis for the methodology and presentation of the data (17). To present the structure of our network, we produced a network diagram of direct comparisons for each outcome. To show to which extent the direct and indirect comparisons of the included interventions contributed to the summary effect, we produced a contribution matrix. We performed NMA using STATA network meta commands, which fits a multivariable random effects meta-analysis. We presented forest plots of the treatment effects and their 95% CIs between different methods of TTM for the outcomes "good neurologic outcome" and "survival." The particularity is that the comparisons between two cooling methods also take into account the indirect effect of the third cooling method on the other two cooling methods. The overall effect between two cooling methods includes the effect of direct comparisons and indirect comparisons. We presented rankograms providing information on the probability of the methods of TTM being ranked first, second, and third best interventions. All analyses were conducted using Stata/IC 16.1 (StataCorp LLC, College Station, TX).

Missing Data and Assessment of Validity of Network Meta-Analysis. We contacted the authors for missing data. An assessment of loss to follow-up was part of our quality assessment. We performed global and local inconsistency tests and assessed clinical heterogeneity as well as statistical heterogeneity for each pairwise comparison.

Sensitivity Analysis. We included randomized and nonrandomized trials, resulting in a wide spectrum of expected level of bias. We performed a sensitivity analysis, including only RCTs (18).

RESULTS

Study Selection

The study selection process is shown in **Supplemental Figure 1**, (http://links.lww.com/CCM/H6; **legend**, http://links.lww.com/CCM/H12). After removing duplicates, our first search resulted in 15,618 records, and after the title and abstract screening, a total of 50 articles were assessed for eligibility. Of these, 30 further studies (one RCT [19] and 29 non-RCTs) were excluded after the full-text screening. Three non-RCTs were partially using the same data from the Korean Centers for Disease Control and Prevention out-of-hospital cardiac arrest registry (20–22). We included the study with most comprehensive study database (22). We continued with 20 studies for the RoB assessment.

Risk of Bias and Level of Evidence

Supplemental Table 1 (http://links.lww.com/CCM/H7; legend, http://links.lww.com/CCM/H12) shows the summarized assessment for risk of bias in a risk of bias summary and a risk of bias graph. Overall, six non-RCTs (23–28) showed critical risk of bias and were excluded. This left a total of 14 studies for the final meta-analysis. Four of these studies were RCTs (29–32), and the other 10 studies were retrospective and prospective observational studies (22, 33–41) (**Supplemental Table 2**, http://links.lww.com/CCM/H8; legend, http://links.lww.com/CCM/H12).

Characteristics of the Studies Included in Final Analysis

The main characteristics of the 14 included studies are shown in Supplemental Table 2 (http://links.lww.com/CCM/H8; legend, http://links.lww.com/CCM/H12). These studies were published between 2008 and 2019, altogether involving 4,062 patients. One study (38) did not report information concerning temperature feedback in 685 patients leaving 3,377 patients for final analysis in our NMA. Overall, 1,160 patients (34%) from 12 studies (22, 29, 31–38, 40, 41) were cooled with intravascular cooling methods and 2,217 patients (66%) from 14 studies (22, 29–41) were cooled with surface cooling methods. Of the 2,217 patients cooled with surface cooling methods, 512 patients from nine studies (30–32, 34, 36, 38–41) were cooled with temperature feedback (23% of patients with surface cooling and 15% of all patients) and 1,705 patients from seven studies (22, 29, 30, 33, 35, 37, 39) were cooled without temperature feedback (77% of patients with surface cooling and 50% of all patients). The sample size of the studies ranged from 41 to 1,762 patients (patients without information on temperature feedback excluded).

Network Meta-Analysis

Network geometry for neurologic outcome and survival is displayed in **Supplemental Figure 2** (http://links.lww.com/CCM/H9; legend, http://links.lww.com/CCM/H12). For neurologic outcome, six studies including 878 patients compared intravascular cooling with surface cooling with temperature feedback, four studies including 2,294 patients compared intravascular cooling with surface cooling without temperature feedback, and two studies including 115 patients compared surface cooling with temperature feedback and surface cooling without temperature feedback. For survival, the network geometry shows a similar result: seven studies including 927 patients compared intravascular cooling with surface cooling with temperature feedback, five studies including 2,335 patients compared intravascular cooling with surface cooling without temperature feedback, and two studies including 115 patients compared surface cooling with temperature feedback with surface cooling without temperature feedback. **Figure 1** shows the forest plots for the overall treatment effects of the three cooling methods, including direct and indirect comparisons between cooling methods, on neurologic outcome and survival. Intravascular cooling compared with surface cooling without temperature feedback was significantly associated with better neurologic outcome (odds ratio [OR], 0.6; 95% CI, 0.49–0.74) and survival (OR, 0.8; 95% CI, 0.66–0.96). Intravascular cooling compared with surface cooling with temperature feedback, and surface cooling with temperature feedback compared with surface cooling without temperature feedback did not show significant differences in neurologic outcome and survival.

Figure 2 shows the contribution matrix, which demonstrates to which extent direct and indirect comparisons of the included interventions contributed to the overall summary estimates for both neurologic outcome and survival. Studies comparing intravascular cooling with surface cooling with temperature feedback, and studies comparing intravascular cooling with surface cooling without temperature feedback equally contributed to the summary estimates, whereas studies comparing surface cooling with temperature feedback with surface cooling without temperature feedback contributed only marginally to the summary estimates.

Figure 3 shows the rankograms of all three treatments: intravascular cooling had the highest probability to be the most beneficial cooling method, followed by surface cooling with temperature feedback and surface cooling without temperature feedback.

Results of global and local inconsistency tests showed that the consistency assumption could be accepted for all treatment contrasts within the network for neurologic outcome and survival. I^2 for each pairwise comparison was 0%.

Sensitivity Analysis

In the sensitivity analysis including only RCTs, there was no change of the direction and only a slight change in the magnitude of the summary effects of the comparisons in the network (**Fig. 4**). I^2 for each pairwise comparison was 0%.

DISCUSSION

This is the first NMA on cooling methods in patients resuscitated from CA and treated with TTM at

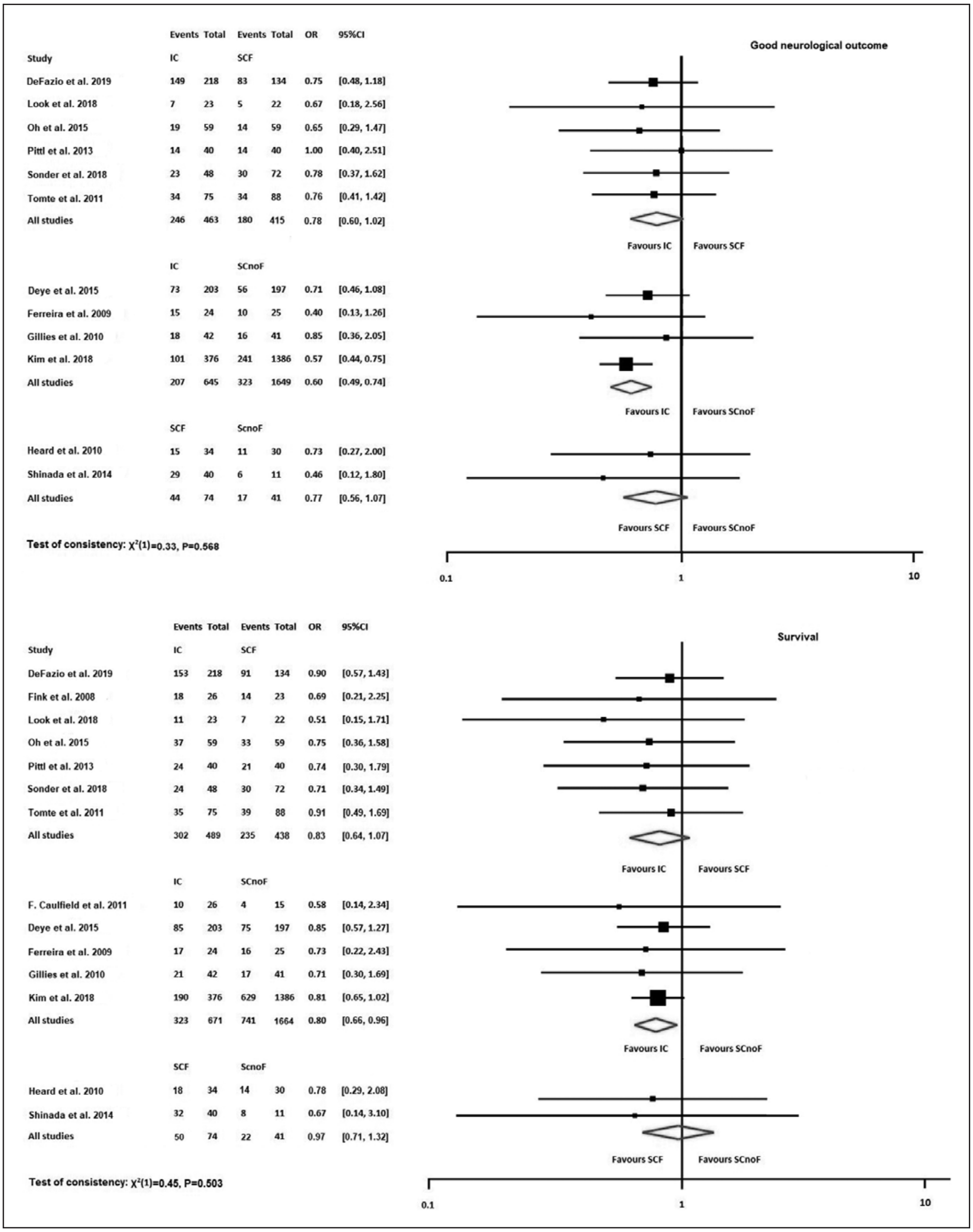

Figure 1. Network meta-analysis forest plot of treatment effects between methods of targeted temperature management on good neurologic outcome and survival. I^2 for each pairwise comparison was 0%. IC = intravascular cooling, OR = odds ratio, SCF = surface cooling with temperature feedback, SCnoF = surface cooling without temperature feedback.

32–34°C, taking into account not only direct comparisons, but also indirect comparisons between three cooling methods: intravascular cooling, surface cooling with temperature feedback, and surface cooling without temperature feedback. Our results indicate that invasive cooling might be the cooling method with the highest probability to result in good neurologic outcome and survival in patients resuscitated from CA and treated with TTM (Fig. 3).

Previous meta-analyses (4–7) investigating the effect of cooling methods on neurologic outcome and survival in CA patients concentrated mainly on the comparison between intravascular cooling and surface cooling but did not further differentiate whether surface cooling was applied with or without automatic temperature feedback control. This differentiation is of importance. Although a stable core temperature over 24 hours can be achieved with surface cooling without temperature feedback by medical staff through regular temperature measurements and appropriate manual adjustment of the cooling intensity in highly specialized centers (42, 43), other studies showed that maintaining a stable core temperature without automatic temperature feedback might be challenging (8–10). Since a stable target temperature during TTM was shown to be independently associated with favorable neurologic outcome (11), a cooling method with automatic temperature feedback might be preferable.

Three meta-analyses showed that invasive cooling was associated with improved neurologic outcome compared with surface cooling (5–7). However, in each

Direct comparison in the network for good neurological outcome	IC vs. SCF	IC vs. SCnoF	SCF vs. SCnoF
Network meta-analysis estimates			
Mixed estimates			
IC vs. SCF	81.6 %	9.2 %	9.2 %
IC vs. SCnoF	5.6 %	88.9 %	5.6 %
SCF vs. SCnoF	45.6 %	45.6 %	8.7 %
Indirect estimates			
Entire network	44.9 %	47.1 %	8.0 %
Included studies	6	4	2

Direct comparison in the network for survival	IC vs. SCF	IC vs. SCnoF	SCF vs. SCnoF
Network meta-analysis estimates			
Mixed estimates			
IC vs. SCF	83.1 %	8.5 %	8.5 %
IC vs. SCnoF	4.3 %	91.4 %	4.3 %
SCF vs. SCnoF	46.3 %	46.3 %	7.4 %
Indirect estimates			
Entire network	45.4 %	47.8 %	6.9 %
Included studies	7	5	2

Figure 2. Contribution matrix for the network on intravascular cooling (IC), surface cooling with temperature feedback (SCF), and surface cooling without temperature feedback (SCnoF) after cardiac arrest. The numbers in the box "Network meta-analysis estimates" and "Entire network" represent percentages. In the box "Entire network," the numbers represent the contributions of each direct comparison to the entire network (the sum of the row is equal to 100%). In the box "Network meta-analysis estimates," the numbers represent the contribution of the direct comparisons to the combined treatment effect of each comparison in the entire network (the sum of each row is equal to 100%). The numbers read as following (for good neurologic outcome): in the row "entire network," the direct comparison IC versus SCF contributed with 44.9%, the direct comparison IC versus SCnoF contributed with 47.1%, and the direct comparison SCF versus SCnoF contributed with 8% to the entire network. In the rows "network meta-analysis estimates," the direct comparison IC versus SCF contributed with 81.6%, the direct comparison IC versus SCnoF contributed with 9.2%, and the direct comparison SCF versus SCnoF contributed with 9.2% to the total effect of the network comparison IC versus SCF, the direct comparison IC versus SCF contributed with 5.6%, the direct comparison IC versus SCnoF contributed with 88.9%, and the direct comparison SCF versus SCnoF contributed with 5.6% to the total effect of the network comparison IC versus SCnoF; the direct comparison IC versus SCF contributed with 45.6%, the direct comparison IC versus SCnoF contributed with 45.6%, and the direct comparison SCF versus SCnoF contributed with 8.7% to the total effect of the network comparison SCF versus SCnoF. The numbers for survival should be read analogous to good neurologic outcome.

meta-analysis, approximately 50% of the studies included surface cooling methods without temperature feedback or both methods, surface cooling with temperature feedback and surface cooling without temperature feedback. The meta-analysis by Kim et al (4) did not find a difference in neurologic outcome between surface cooling and invasive cooling; however, some of the individual study results presented in Figure 2 of this study seem not to match the results of the original publication, leaving the interpretation of the result of this meta-analysis study unclear. The meta-analysis by Calabró et al (6) is differentiated in a subgroup analysis between cooling methods with and without temperature feedback and found that cooling with temperature feedback was associated with improved neurologic outcome.

There are only few single studies specifically comparing intravascular cooling with surface cooling with temperature feedback (22, 29, 31–38, 40, 41). The majority of these studies showed that there may be a trend for improved neurologic outcome in patients cooled with intravascular cooling compared with surface cooling with temperature feedback. However, it remains unclear if the lack of statistical significance is due to the low patient number or if there is truly no effect. The meta-analysis by Liao et al (7) compared in a subgroup analysis intravascular cooling with a group using a specific surface cooling device with

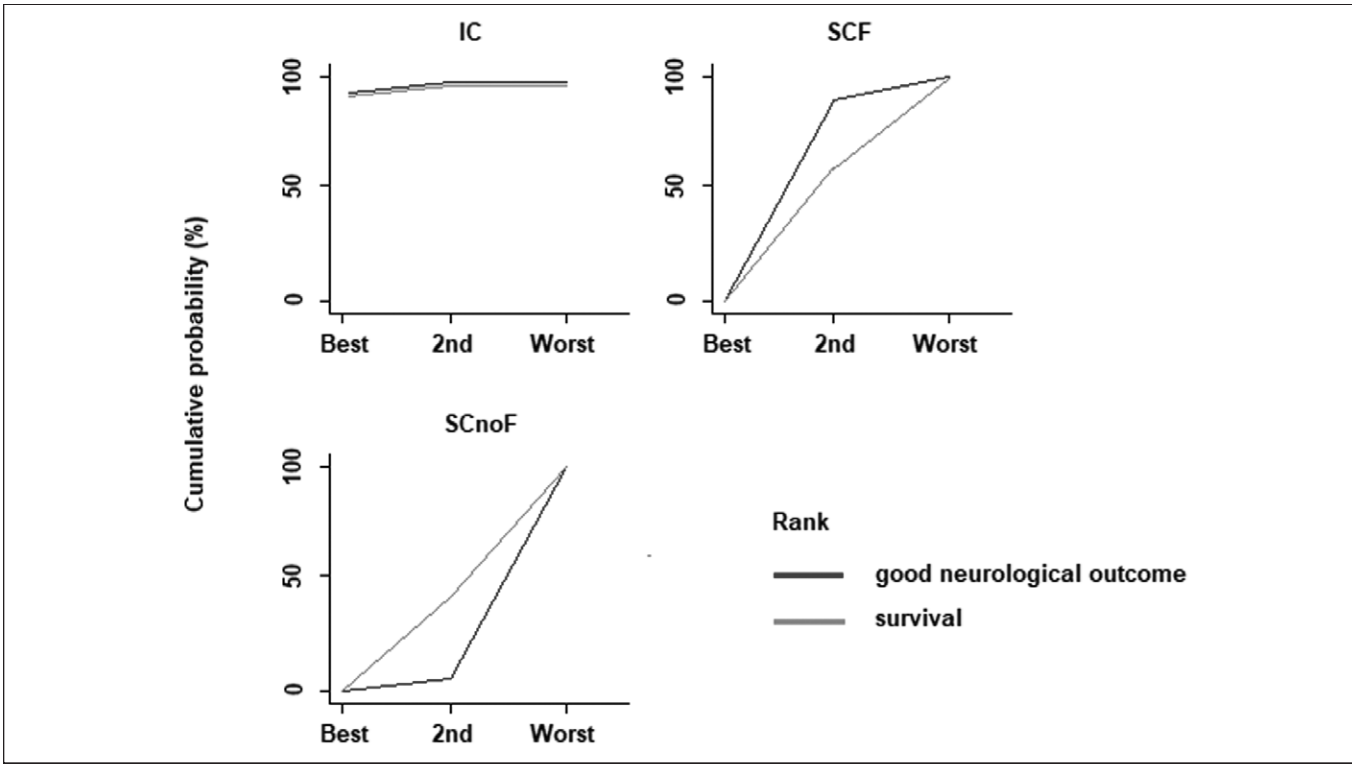

Figure 3. Rankograms of probabilities of methods of targeted temperature management for being best, second or third best for good neurologic outcome and survival. IC = intravascular cooling, SCF = surface cooling with temperature feedback, SCnoF = surface cooling without temperature feedback.

temperature feedback, namely Arctic-Sun temperature management system. The authors of this study found that intravascular cooling significantly improved neurologic outcome compared with non-Artic Sun surface cooling and a trend toward better neurologic outcome compared with Artic-Sun cooling (Medivance Inc., Louisville, CO). However, the study selection for this subgroup analysis is unclear, since studies including additional surface cooling devices were allocated to the Arctic-Sun group, and other studies including the Artic-Sun were allocated to the non-Arctic-Sun group, leaving the interpretation of the results of this meta-analysis study unclear.

Our study is the first NMA, differentiating between the effects of temperature feedback and no temperature feedback in the surface cooling groups for neurologic outcome and survival in patients resuscitated from CA and treated with TTM. The NMA aims to examine clinical evidence from direct and indirect treatment comparisons in a network of treatments and related studies (44). Network meta-analyses are useful for assessing the comparative effects of several competing interventions in clinical practice and are a valuable tool for health technology assessment and comparative effectiveness research (44). We found that intravascular cooling compared with surface cooling without temperature feedback was significantly associated with improved neurologic outcome and survival. Additionally, we did not find significant differences of intravascular cooling compared with surface cooling with temperature feedback, and surface cooling with temperature feedback compared with surface cooling without temperature feedback in neurologic outcome and survival (Fig. 1). The rankograms for the TTM cooling methods network suggest that intravascular cooling had the highest probability of being the most beneficial intervention for neurologic outcome and survival, followed by surface cooling with temperature feedback, whereas surface cooling without temperature feedback had the highest probability of being least beneficial (Fig. 3).

One explanation for a possible better outcome in patients cooled with intravascular cooling compared with surface cooling with temperature feedback might be the ability of intravascular cooling devices to react more quickly to the temperature feedback mechanism, resulting in a faster adjustment of the patient's target body temperature, less temperature fluctuations, and less overcooling/undercooling/unexpected rewarming events (32). At the same time, intravascular cooling

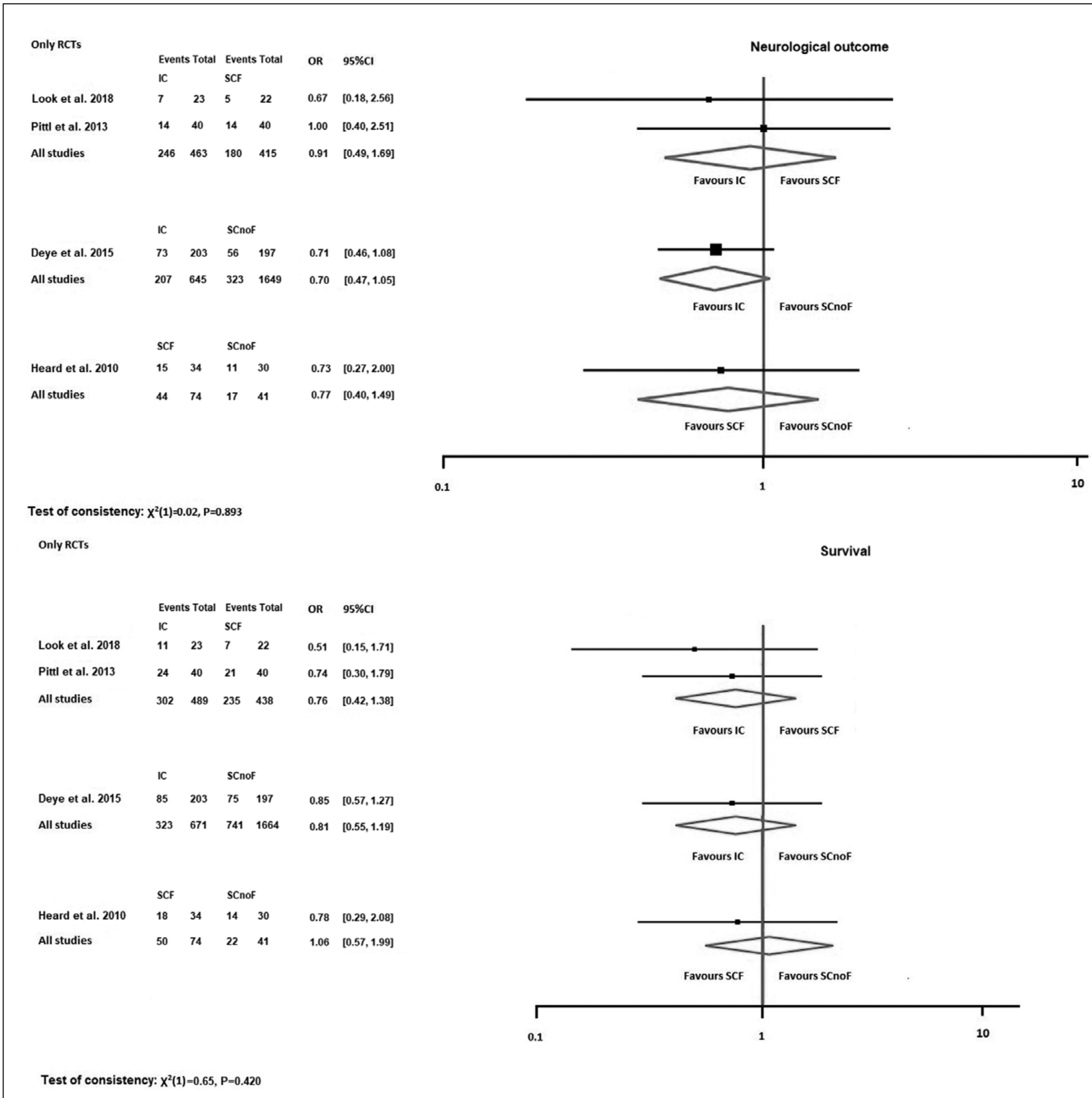

Figure 4. Network meta-analysis forest plot of treatment effects between methods of targeted temperature management on good neurologic outcome and survival restricted to randomized clinical trials (RCTs). I^2 for each pairwise comparison was 0%. IC = intravascular cooling, OR = odds ratio, SCF = surface cooling with temperature feedback, SCnoF = surface cooling without temperature feedback.

is associated with a certain rate of infection, hemorrhage, and catheter related thrombosis, which might cause pulmonary embolism (32, 45–48). Taking into account the potential complications of intravascular cooling devices, the use of a surface cooling device with temperature feedback should be considered as a safe alternative.

Comparing our search results with the results of four related meta-analyses (4–7), it is noticeable that all studies included in the four meta-analyses were initially found and taken into account in our literature search. From studies partially included in the other meta-analysis (4–7), we excluded seven studies due to unclear information on temperature feedback (10, 19, 49–53), and further six studies due to critical risk of bias (23–28). As opposed to our meta-analysis, eight studies (29, 30, 33, 35–39) were not included in the other meta-analyses (4–7) and seven studies (29, 30, 33, 35, 37–39) for unknown reasons and one study (36) due to language restrictions. A detailed comparison table of included and excluded studies of the previous meta-analyses as compared with our meta-analysis is shown in **Supplemental Table 3** (http://links.lww.com/CCM/H10; legend, http://links.lww.com/CCM/H12) and **Supplemental Table 4** (http://links.lww.com/CCM/H11; legend, http://links.lww.com/CCM/H12).

In the TTM2 trial, no difference in outcome between the two temperature levels was found, reactive fever control (normothermia) did not lead to better outcomes than 33°C, and 33°C did not result in worse outcomes. However, the possible better outcome in patients cooled with intravascular cooling shown in our study emphasizes the utility of TTM at 33°C in appropriate patients as determined by the treating team. In addition, normothermia without a cooling method is not easy to achieve, resulting in increased rates of fever, potentially associated with worse outcome (54).

We identified the following study limitations: First, we did not control for factors known to be associated with outcome, such as initial rhythm, bystander cardiopulmonary resuscitation, no-flow time, or low-flow time. Second, the studies included are from different countries all over the world, with differences due to socioeconomic status and racial properties of the population. Third, the sample sizes of included studies as well as included patients numbers vary between the three TTM groups, with the potential of lack of power to prove a meaningful clinical difference in outcome. Fourth, most of the included studies were non-RCTs, some of them with a serious risk of bias, which may affect the confidence in our conclusion. Fifth, all studies in our analysis targeted a temperature range of 32–34°C; thus, the results of our analysis apply only to patients treated in this temperature range. Future studies are needed to investigate whether the choice of cooling method is associated with outcome also in patients with TTM at normothermia. Sixth, other parameters of temperature control such as time to start cooling, cooling duration, or rewarming rate might be associated with outcome; however, these data were not available in all studies and thus not analyzed. An additional limitation of the study is that we did not evaluate cooling device performance. Whether cooling device performance impacts outcome needs to be investigated in further studies, preferably as individual patient data meta-analysis.

CONCLUSIONS

The results of our network meta-analysis suggest that in patients treated with TTM at 32–34°C after CA, intravascular cooling has the highest probability of being the most beneficial cooling method for neurologic outcome and survival, followed by surface cooling with temperature feedback, whereas surface cooling without temperature feedback has the highest probability of being least beneficial. Further large RCTs comparing the effect of endovascular cooling with surface cooling with temperature feedback at different temperature levels of TTM on neurologic outcome are needed.

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Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (http://journals.lww.com/ccmjournal).

Drs. Arrich and Behringer formulated the aim of the study. Drs. Ramadanov and Klein did the literature search and study selection. Drs. Arrich and Herkner performed all statistical analysis. Drs. Ramadanov and Arrich created all figures and tables. Dr. Ramadanov wrote the draft of the article. All authors provided critical feedback to the article and approved the final version.

Dr. Behringer received speaker's fees from ZOLL, BD, and EMCOOLS. The remaining authors have disclosed that they do not have any potential conflicts of interest.

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