Anesthesiology 2010; 112:86–101

No Association between Intraoperative Hypothermia or Supplemental Protective Drug and Neurologic Outcomes in Patients Undergoing Temporary Clipping during Cerebral Aneurysm Surgery

Findings from the Intraoperative Hypothermia for Aneurysm Surgery Trial

Bradley J. Hindman, M.D.,* Emine O. Bayman, Ph.D.,† Wolfgang K. Pfisterer, M.D.,‡ James C. Torner, Ph.D.,§ Michael M. Todd, M.D.‖; on behalf of the IHAST Investigators#

ABSTRACT

Background: Although hypothermia and barbiturates improve neurologic outcomes in animal temporary focal ischemia models, the clinical efficacy of these interventions during temporary occlusion of the cerebral vasculature during intracranial aneurysm surgery (temporary clipping) is not established.

Methods: A *post hoc* analysis of patients from the Intraoperative Hypothermia for Aneurysm Surgery Trial who underwent temporary clipping was performed. Univariate and multivariate logistic regression methods were used to test for associations between hypothermia, supplemental protective drug, and short- (24-h) and long-term (3-month) neurologic outcomes. An odds ratio more than 1 denotes better outcome.

Results: Patients undergoing temporary clipping (n = 441) were assigned to intraoperative hypothermia (33.3° ± 0.8°C, n = 208) or normothermia (36.7° ± 0.5°C, n = 233), with 178 patients also receiving supplemental protective drug (thiopental or etomidate) during temporary clipping. Three months after surgery, 278 patients (63%) had good outcome (Glasgow Outcome Score = 1). Neither hypothermia (P = 0.847; odds ratio = 1.043, 95% CI = 0.678–1.606) nor supplemental protective drug (P = 0.835; odds ratio = 1.048, 95% CI = 0.674–1.631) were associated with 3-month Glasgow Outcome Score. The effect of supplemental protective drug did not significantly vary with temperature. The effects of hypothermia and protective drug did not significantly vary with temporary clip duration. Similar findings were made for 24-h neurologic status and 3-month Neuropsychological Composite Score.

Conclusion: In the Intraoperative Hypothermia for Aneurysm Surgery Trial, neither systemic hypothermia nor supplemental protective drug affected short- or long-term neurologic outcomes of patients undergoing temporary clipping.

What We Already Know about This Topic

- Animal studies suggest that hypothermia and barbiturates protect the brain during transient focal ischemia, but the clinical relevance of this is unknown

What This Article Tells Us That Is New

- In a secondary analysis of 441 patients with temporary clipping during cerebral aneurysm surgery, neither hypothermia nor barbiturate treatment improved 24-h or 3-month neurologic outcome
- As opposed to results in animal studies, these interventions may not be protective in patients undergoing this procedure

TEMPORARY occlusion of the cerebral vasculature ("temporary clipping") is commonly used during intracranial aneurysm surgery. Numerous reports address potential adverse effects of temporary clipping, primarily focal cerebral ischemia and associated neurologic injury.[1–9] A fundamental question is whether intraoperative interven-

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org).

* Professor and Vice-Chair (Faculty Development), ‖ Professor and Head, Department of Anesthesia, University of Iowa Roy J. and Lucille A. Carver College of Medicine. † Associate, Department of Anesthesia, University of Iowa Roy J. and Lucille A. Carver College of Medicine and Department of Biostatistics, College of Public Health, University of Iowa. ‡ University Lecturer, Medical University of Vienna, and Vice-Chair, Department of Neurosurgery, Sozialmedizinisches Zentrum-Ost, Donauspital, Vienna, Austria. § Professor and Head, Department of Epidemiology, University of Iowa College of Public Health, University of Iowa. # Members of the IHAST Investigators are listed in the appendix.

Received from Department of Anesthesia, Carver College of Medicine and the Department of Epidemiology, College of Public Health, University of Iowa, Iowa City, Iowa. Submitted for publication June 7, 2009. Accepted for publication October 6, 2009. Supported by grant No. R01 NS38554 from the National Institute of Neurological Disease and Stroke, Bethesda, Maryland (to M.M.T.). Additional funding was provided by the Department of Anesthesia, The University of Iowa Roy J. and Lucille A. Carver College of Medicine, Iowa City, Iowa.

Address correspondence to Dr. Hindman: Department of Anesthesia, University of Iowa Hospitals and Clinics, Iowa City, Iowa 52242. brad-hindman@uiowa.edu.

tions proposed to have protective efficacy in the setting of temporary focal ischemia (*e.g.*, hypothermia and/or protective drugs) actually improve neurologic outcomes in patients undergoing temporary clipping.

The Intraoperative Hypothermia for Aneurysm Surgery Trial (IHAST) was a randomized trial of mild systemic hypothermia (33°C) in patients undergoing surgery to treat an acutely ruptured intracranial aneurysm. In the entire cohort (n = 1,000 patients), hypothermia did not significantly affect neurologic or neuropsychologic outcomes.[10,11] However, in these previous reports, IHAST patients undergoing temporary clipping were not analyzed separately. Patients undergoing temporary clipping may be the most appropriate subgroup in whom the effect of potentially protective interventions may be assessed. Therefore, the aim of this study was to reexamine IHAST data to determine whether intraoperative hypothermia was associated with altered outcomes in patients undergoing temporary clipping.

In IHAST, two potentially protective interventions could be used simultaneously during temporary clipping, namely, hypothermia (*vs.* normothermia) and supplemental protective drug (*vs.* no protective drug). This adds complexity to the analysis because both hypothermia and supplemental protective drug may affect outcome, and these two interventions could interact. For example, the effect of supplemental protective drug could be temperature dependent (*i.e.*, protective drug might improve outcome when given during normothermia but have no effect when given during hypothermia or *vice versa*). An additional factor to be considered is temporary clip duration. Brief temporary clip durations may be less likely to result in neurologic injury than longer clip durations, whereas very long clip durations may not be amenable to intervention. Therefore, in this analysis, we assess the potential interactions among these factors (temperature, supplemental protective drug, and temporary clip duration) to determine whether intraoperative protective interventions—either hypothermia or supplemental protective drug—were associated with altered neurologic outcomes.

Materials and Methods

IHAST Protocols and Methods

IHAST was a multicenter, prospective, randomized, partially blinded trial designed to determine whether mild intraoperative systemic hypothermia (33°C) would result in improved neurologic outcome in patients undergoing surgery to treat acutely ruptured intracranial aneurysms as compared with intraoperative normothermia. Details of trial design, patient eligibility, protocols, and outcome assessment have been published previously.[10,11] In brief, between February 2000 and April 2003, nonpregnant adults with subarachnoid hemorrhage (SAH) and an angiographically confirmed intracranial aneurysm scheduled to undergo surgical treatment within 14 days of SAH were eligible to participate. Other major inclusion criteria included a preoperative World Federation of Neurologic Surgeons (WFNS) Class of I, II, or III[12] and not being tracheally intubated at the time of study enrollment. IHAST protocols were approved by the Human Subjects' Committees at each participating center, and written informed consent was obtained from either the patients or their families. Data collection included patient demographics and pre-SAH medical history. Information regarding the characteristics of the ruptured aneurysm (location and angiographic diameter) and its immediate effects (amount of subarachnoid blood [Fisher Scale],[13] WFNS class, and National Institute of Health (NIH) Stroke Scale[14]) were recorded before surgery.

Anesthesia was induced with thiopental or etomidate and maintained with isoflurane or desflurane, fentanyl or remifentanil, and nitrous oxide or air with oxygen. Use of intraoperative neurologic monitoring (*e.g.*, electroencephalography and evoked potentials) was determined by the preferences of each operating team. After induction of general anesthesia, patients were randomized to one of two groups: (1) hypothermia (target esophageal temperature 33°C) or (2) normothermia (target esophageal temperature 36.5°C), which were achieved with surface techniques. The knowledge of intraoperative temperature was limited to each patient's anesthesiologist; surgeons were not informed of the patient's temperature. Rewarming of hypothermic patients began after the last aneurysm had been secured and was largely complete by 2 h after surgery.

Intraoperative surgical management consisted primarily of clipping the ruptured aneurysm. The decision to use temporary clipping was at the discretion of the neurosurgeon and was defined as the temporary occlusion of any major intracranial vessel for more than or equal to 1 min (n = 441); this defined our study population. Temporary clip duration was the sum of all occlusion durations in all arterial territories. However, in 96% of patients, temporary clipping took place in only a single arterial distribution. For this analysis, temporary clip duration was categorized as brief (≤ 10 min), intermediate (11–19 min), or long (≥ 20 min) on the basis of convention, clinical experience, and previous reports.[1–4,7] Although approximately 10% of patients had more than one aneurysm treated during surgery, the first aneurysm treated (Aneurysm 1) was responsible for the presenting SAH in 96% of patients. Accordingly, aneurysm characteristics and intraoperative status at the time of temporary clipping are referenced to completion of clipping of Aneurysm 1. The indications, choice (thiopental or etomidate), and dose of the supplemental protective drug administered during temporary clipping were determined by the preferences of each operating team.

All data collection, pre- and postoperative management decisions, and outcome assessments were made by individuals who had no knowledge of intraoperative temperature assignment or supplemental protective drug administration. At every patient encounter, patients were assessed for the occurrence of any of the 106 predefined adverse events or procedures collectively referred to as intercurrent events. Each intercurrent event had defined diagnostic criteria based

on available guidelines, standards, or consensus statements. Pre- and postoperative management was not standardized, but all aspects of treatment and patient condition were prospectively documented daily for either 14 days or until discharge (if discharge occurred before 14 days). Final neurologic and neuropsychologic outcome assessments were made approximately 3 months after surgery by certified examiners.

Outcome Measures

In IHAST, the primary outcome measure was the five-point modified Glasgow Outcome Score (GOS),[15] which was obtained in 1,000 patients (1 = good recovery, 2 = moderate disability, 3 = severe disability, 4 = vegetative state, and 5 = death).[16] For this analysis, the 3-month GOS was dichotomized as either 1 (good recovery) or more than 1 (incorporating all levels of disability and death).

A neuropsychologic assessment was also conducted 3 months after surgery. The details regarding this assessment have been previously reported.[11] The test battery included the Benton Visual Retention Test,[17] Controlled Oral Word Association,[18] Rey-Osterrieth Complex Figure-Copy,[19] Grooved Pegboard, and Trail Making Test.[19,20] Test performance was compared with age- and education-adjusted normative data. The results were converted to *T* scores, and individual *T* scores were then averaged to provide a Neuropsychological Composite Score, providing an index of global cognitive status. If not all tests were completed, a composite score was calculated based on the tests that were completed, provided that at least three scores were available. Impairment on the composite score was defined as a *T* score of 30 or less, which is 2 SD below the population norm. If less than three neuropsychologic tests were completed, a composite score was not calculated, but patients were classified as either globally impaired or not impaired by an imputation process based on other neurologic assessments.[11] In the temporary clip population, 21 Composite Scores were imputed: 10 with no impairment and 11 with impairment. For this analysis, 3-month Neuropsychological Composite Score was dichotomized as either normal (not impaired) or abnormal (impaired). Temporary clip patients who had died by 3 months (n = 33) did not have Neuropsychological Composite Score and were not included in the analysis of this outcome measure.

Because neurologic injuries evolve for many days or weeks after an insult, interventions that improve short-term neurologic outcome may not have a sustained long-term benefit.[21,22] In addition, postoperative events such as vasospasm or fever[23] could negate the effect of an otherwise effective intraoperative protective intervention. For these reasons, associations between protective interventions and early postoperative outcome were also assessed. For this analysis, neurologic deterioration at 24 h after surgery was selected as the early outcome measure. Neurologic deterioration at 24 h after surgery was defined by the presence of any one or more of the following conditions at that time: (1) a decrease of two or more points on the Glasgow Coma Scale as compared with the preoperative value; (2) an increase of four or more points on the NIH Stroke Scale as compared with the preoperative value; (3) an increase of one or more points on the motor component of any limb on the NIH Stroke Scale as compared with the preoperative value; (4) tracheal intubation; (5) death; (6) report of a new focal neurologic deficit within the first 2 h of surgery by the anesthesiologist; and (7) the diagnosis of delayed ischemic neurologic deficit. Compared with patients who had no neurologic deterioration at 24 h (n = 244), patients with neurologic deterioration (n = 197) had a greater incidence of (1) postoperative cerebral infarction (16% *vs.* 44%, respectively, $P < 0.0001$), (2) nonfatal disability at 3 months (21% *vs.* 40%, respectively, $P < 0.0001$), and (3) mortality at 3 months (0.4% *vs.* 16%, respectively, $P < 0.0001$). For this analysis, this early outcome measure was dichotomized as either no neurologic deterioration at 24 h or neurologic deterioration.

Statistical Methods

All data entry was performed by the Data Management Center at the University of Iowa. Statistical analyses were performed on SAS 9.1.3 Service Pack XP PRO Platform (SAS Institute, Inc., Cary, NC). Power analyses were performed using nQuery Advisor, 7.0 (Statistical Solutions, Ltd., Cork, Ireland). The univariate tests used included the Fisher exact test, Pearson chi-square test, Kruskal-Wallis test, and Wilcoxon rank sum test depending on the characteristics and distribution of the data.

Logistic regression analysis was conducted on the basis of good outcome. A variable associated with an increased likelihood of a good outcome was considered to be "protective" and had an odds ratio (OR) more than 1. Conversely, variables associated with a decreased likelihood of good outcome were detrimental and had an OR less than 1. For each of the three outcome measures, three sets of logistic regression analyses were sequentially developed and referred to as Steps 1–3.

In Step 1, logistic regression was used to test for the presence of interactions between temperature group assignment (hypothermia *vs.* normothermia), supplemental protective drug (supplemental protective drug *vs.* none), and temporary clip duration (long, intermediate, *vs.* brief). Initial models included all interaction terms. Thereafter, in sequential fashion, the interaction term having the greatest nonsignificant *P* value was removed, and the model was then recalculated to assess the effect of removal of the interaction term on the remaining terms. This process was repeated until all interaction terms had a *P* value less than 0.05 or were removed from the model. We observed that no interaction term was significant in any model by using this process. Because there were no significant interaction terms in any of the Step 1 outcome models, Step 2 logistic models included only terms for temperature group assignment, supplemental protective drug, and temporary clip duration category.

In Step 3, logistic models were developed to include and adjust for other potential determinates of outcome (covariates). Variables that were tested included a set of 10 standard

covariates used in previous analysis of IHAST data: gender, race, age, history of hypertension, preoperative WFNS score, preoperative NIH Stroke Scale Score, preoperative Fisher Score, aneurysm location (posterior *vs.* anterior), aneurysm size, and time from SAH to surgery.[23–26] In addition to these standard covariates, 10 other variables were tested that differed as a function of either temperature group assignment, use of supplemental protective drug, and/or temporary clip duration (see Results). These 10 additional variables were preoperative best verbal score, intraoperative aneurysm exposure, intraoperative electroencephalography use, intraoperative evoked potential use, intraoperative central venous pressure monitoring, intraoperative mean arterial pressure, intraoperative blood glucose concentration, intraoperative arterial oxygen partial pressure (Pa_{O_2}), intraoperative blood loss, and total surgery duration. Thus, in total, 20 variables were tested for inclusion in Step 3 outcome models and for their effect on associations between temperature group assignment, supplemental protective drug, temporary clip duration, and the 3 outcome measures. To accomplish this, in Step 3, a forward stepwise model selection process was used, with the forced inclusion of temperature group, supplemental protective drug, and temporary clip duration in all models. For initial model entry, each candidate variable was required to have a P value of less than 0.25, whereas to remain in the final model, a candidate variable was required to have a P value of less than 0.05.

In all analysis, a P value of less than or equal to 0.05 was the threshold for a statistically significant difference or association, without adjustment for multiple comparisons.

Results

Of the 1,000 patients who had 3-month outcome determinations, information regarding the use of temporary clips was missing in 6. Of the remaining 994 patients, 441 underwent temporary clipping and 553 did not. Comparisons of patient and aneurysm characteristics, perioperative conditions and events, and neurologic outcomes in patients who underwent temporary clipping and those who did not are provided in Supplemental Digital Content 1, tables S-1 to S-3, respectively, http://links.lww.com/ALN/A561.

Patients who underwent temporary clipping (n = 441) were subgrouped into brief (≤ 10 min, n = 279), intermediate (11–19 min, n = 104), and long (≥ 20 min, n = 58) occlusion durations. As shown in table 1, patient characteristics of these three subgroups did not differ with regard to sex, race, age, history of hypertension, preoperative WFNS or Fisher scores, aneurysm size, or time from SAH to surgery. In contrast, these three subgroups differed in preoperative neurologic status (best verbal response on the Glasgow Coma Scale and NIH Stroke Scale) and aneurysm location. As shown in table 2, intraoperative variables that differed among the three clip duration subgroups included the ease of aneurysm exposure, frequency of intraoperative supplemental protective drug administration, frequency of central venous pressure monitoring, blood glucose concentration, number of permanent clips, frequency of aneurysm wrapping, estimated blood loss (borderline $P = 0.056$), and total surgery duration. As shown in table 3, without adjustment for these covariates, greater postoperative neurologic morbidity and less favorable postoperative neurologic outcomes were associated with greater temporary clip durations. In Step 3 of the multivariate analysis, except for number of permanent clips and frequency of wrapping, all the variables noted previously were tested for their association with outcome and for their effect on associations between protective interventions, temporary clip duration, and outcomes.

Patients were randomized to intraoperative hypothermia or normothermia. Of those who underwent temporary clipping, 208 were assigned to intraoperative hypothermia (33.3° ± 0.8°C) and 233 to normothermia (36.7° ± 0.5°C). The two temperature subgroups did not differ with respect to sex, race, age, history of hypertension, preoperative WFNS, NIH Stroke Scale, or Fisher Scores, aneurysm location, or time from SAH to surgery. Aneurysm angiographic diameter differed slightly between hypothermia and normothermia subgroups (9 ± 6 mm *vs.* 8 ± 5 mm, respectively, Wilcoxon rank sum $P = 0.047$). Four intraoperative variables differed between temperature subgroups: ease of aneurysm exposure, frequency of central venous pressure monitoring, blood glucose concentration, and Pa_{O_2} (each $P < 0.05$; data provided in Supplemental Digital Content 1, table S-4, http://links.lww.com/ALN/A561). In Step 3 of the analysis, all the variables noted previously were tested for their association with outcomes and their effect on associations between protective interventions, temporary clip duration, and outcomes.

Patients undergoing temporary clipping either had no additional protective intervention (n = 263) or received supplemental protective drug during temporary clipping (thiopental, n = 157; etomidate, n = 20; not identified, n = 1). Although not randomized, these two subgroups did not differ with respect to sex, race, age, history of hypertension, preoperative WFNS, NIH Stroke Scale, or Fisher Scores, aneurysm size or location, or time from SAH to surgery. Seven intraoperative variables differed between these two subgroups: use of intraoperative electroencephalography and evoked potential monitoring, frequency of central venous pressure monitoring, mean arterial pressure, blood glucose concentration, Pa_{O_2} (borderline $P = 0.067$), and total surgery duration (each $P < 0.05$; data provided in Supplemental Digital Content 1, table S-5, http://links.lww.com/ALN/A561). In Step 3 of the analysis, all the variables noted previously were tested for their association with outcomes and for their effect on associations between protective interventions, temporary clip duration, and outcomes.

The dose of supplemental thiopental did not differ between normothermic and hypothermic patients (7.4 ± 5.5 mg/kg [n = 93] *vs.* 7.2 ± 5.8 mg/kg [n = 64], respectively, Wilcoxon rank sum $P = 0.701$). Supplemental etomidate dose was greater in normothermic than in hypothermic pa-

Table 1. Patient and Aneurysm Characteristics

Variable	Temporary Clip Duration ≤10 min (n = 279)	11–19 min (n = 104)	≥20 min (n = 58)	*P* Value
Female, n (%)	185 (66)	64 (62)	31 (53)	0.159*
White race, n (%)	224 (80)	85 (82)	49 (85)	0.549*
Age, yr	51 ± 12	52 ± 12	50 ± 11	0.858†
History of hypertension, n (%)	100 (36)	41 (39)	23 (40)	0.736*
Preoperative best verbal—oriented, n (%)	237 (85)	91 (88)	37 (64)	<0.001*
Preoperative WFNS Score, n (%)				
I	192 (69)	72 (69)	32 (55)	0.216*
II	73 (26)	29 (28)	21 (36)	
III	14 (5)	3 (3)	5 (9)	
Preoperative NIH Stroke Scale Score, n (%)				
Incomplete	16 (6)	11 (11)	1 (2)	0.017*
0	162 (58)	48 (46)	27 (47)	
1–7	94 (34)	43 (41)	25 (43)	
8–14	7 (3)	1 (1)	5 (9)	
15–42	0 (0)	1 (1)	0 (0)	
Preoperative Fisher Score, n (%)				
1	17 (6)	9 (9)	1 (2)	0.625*
2	86 (31)	33 (32)	17 (29)	
3	139 (50)	48 (46)	29 (50)	
4	37 (13)	14 (14)	11 (19)	
Aneurysm 1, location, n (%)				
Carotid or ophthalmic	7 (3)	0 (0)	4 (7)	0.005*
Posterior communicating	48 (17)	13 (13)	6 (10)	
Anterior choroidal	3 (1)	4 (4)	1 (2)	
Carotid bifurcation	5 (2)	0 (0)	0 (0)	
Carotid (other)	0 (0)	2 (2)	1 (2)	
Middle cerebral	81 (29)	20 (19)	10 (17)	
Anterior communicating	114 (41)	50 (48)	30 (52)	
Anterior cerebral (other)	9 (3)	4 (4)	1 (2)	
Vertebrobasilar (not PICA)	10 (4)	6 (6)	3 (5)	
PICA	2 (1)	5 (5)	2 (3)	
Aneurysm 1, largest angiographic diameter, mm	8 ± 5	9 ± 6	9 ± 7	0.308†
Time from SAH to surgery, d	3.4 ± 3.1	3.1 ± 3.1	3.2 ± 2.0	0.790†

Continuous variables are expressed as mean ± SD.

* Fisher exact test. † Kruskal-Wallis test.

NIH = National Institutes of Health; PICA = posterior inferior cerebellar artery; SAH = subarachnoid hemorrhage; WFNS = World Federation of Neurological Surgeons.

tients (0.67 ± 0.22 mg/kg, [n = 6] *vs.* 0.40 ± 0.14 mg/kg [n = 13], respectively, Wilcoxon rank sum $P = 0.005$). Supplemental thiopental and etomidate doses did not differ among the three temporary clip duration subgroups (Kruskal-Wallis $P = 0.189$ and 0.277, respectively). Accordingly, the dose of protective drug (in mg/kg) was not included as a covariate in any analysis.

Univariate Analysis

In table 4, unadjusted neurologic outcomes are reported specific to intraoperative temperature subgroup, use of supplemental protective drug, and temporary clip duration subgroup. Within each of the three temporary clip duration subgroups, as well as overall (all clip durations), neurologic outcomes did not differ between hypothermic and normothermic patients (all $P > 0.05$; data provided in Supplemental Digital Content 1, tables S-6 to S-8, http://links.lww.com/ALN/A561). For example, when all temporary clip durations are combined, 64% of normothermia patients (149 of 233) had a 3-month GOS score of 1 as compared with 62% of hypothermia patients (129 of 208); Pearson chi-square $P = 0.675$. Likewise, within each of the three temporary clip duration subgroups, as well as overall, neurologic outcomes did not differ between patients who received supplemental protective drug and those who did not, regardless of temperature group. Increasing temporary clip duration was associated with a less favorable outcome in some comparisons. For example, in all normothermia patients, the percentage of patients with good 24-h neurologic status decreased with increasing temporary clip duration; Pearson chi-square $P = 0.030$.

Multivariate Logistic Analysis

Multivariate analysis was used to determine whether there were any significant interactions between temperature group assignment, supplemental protective drug, and temporary

Table 2. Perioperative Conditions and Events

Variable	Temporary Clip Duration ≤10 min (n = 279)	11–19 min (n = 104)	≥20 min (n = 58)	*P* Value
Intraoperative aneurysm exposure, n (%)				
Easy	35 (13)	11 (12)	4 (7)	<0.001*
Moderate	135 (48)	43 (41)	12 (21)	
Difficult	83 (30)	33 (32)	22 (38)	
Very difficult	26 (9)	17 (16)	20 (35)	
Supplemental protective drug given, n (%)	93 (33)	55 (53)†	30 (52)	<0.001*
Thiopental dose, mg/kg (n)	6.8 ± 5.0 (87)	6.8 ± 5.3 (45)	9.9 ± 7.7 (25)	0.189‡
Etomidate dose, mg/kg (n)	0.52 ± 0.33 (5)§	0.43 ± 0.15 (9)	0.56 ± 0.12 (5)	0.277‡
Intraoperative electroencephalographic monitoring, n (%)	44 (16)	23 (22)	11 (19)	0.310*
Intraoperative evoked potential monitoring, n (%)	58 (21)	29 (28)	14 (24)	0.319*
Intraoperative central venous pressure monitoring, n (%)	153 (55)	40 (39)	36 (62)	0.004*
Aneurysm 1, patient temperature				
Normothermia, °C (n)	36.7 ± 0.5 (152)	36.7 ± 0.4 (50)	36.6 ± 0.6 (31)	0.911‡
Hypothermia, °C (n)	33.3 ± 0.9 (127)	33.3 ± 0.9 (54)	33.2 ± 0.6 (27)	0.962‡
Aneurysm 1, mean arterial pressure, mmHg	80 ± 14	80 ± 15	77 ± 15	0.255‡
Aneurysm 1, blood glucose, mg/dl	130 ± 34	141 ± 38	133 ± 40	0.017‡
Aneurysm 1, arterial PO2, mmHg	216 ± 109	223 ± 111	217 ± 105	0.746‡
Aneurysm 1, permanent clips applied	1.4 ± 0.7	1.5 ± 0.8	1.7 ± 0.9	0.012‡
Aneurysm 1, wrapped, n (%)	12 (4)	4 (4)	8 (14)	0.021*
Aneurysm 1, intraoperative leak or rupture, n (%)	121 (43)	49 (47)	33 (57)	0.174*
Intraoperative blood loss, ml	455 ± 420	452 ± 310	605 ± 528	0.056‡
Intraoperative RBC administration, n (%)	41 (15)	11 (11)	12 (21)	0.220*
Patient temperature at the end of surgery				
Normothermia, °C (n)	36.8 ± 0.5 (152)	36.9 ± 0.5 (50)	36.8 ± 0.5 (31)	0.190‡
Hypothermia, °C (n)	34.4 ± 0.9 (127)	34.4 ± 1.0 (54)	34.6 ± 1.0 (26)	0.681‡
Total surgery duration, min	323 ± 101	342 ± 108	372 ± 94	<0.001‡
Patient temperature 2 h after the end of surgery				
Normothermia, °C (n)	37.1 ± 0.7 (152)	37.6 ± 0.7 (50)	37.4 ± 0.6 (31)	0.061‡
Hypothermia, °C (n)	36.5 ± 1.0 (127)	36.4 ± 1.2 (54)	36.9 ± 1.0 (26)	0.087‡

Continuous variables are expressed as mean ± SD.

* Fisher exact test. † One patient with missing values for supplemental protective drug type and dose. ‡ Kruskal-Wallis test. § One of six etomidate patients had the dose reported as 0 mg; dose calculated for five patients.

clip duration. As summarized in table 5, there were no significant interaction terms in any of the three Step 1 outcome models, and subsequent serial removal of interaction terms did not result in any new significant interaction terms. Therefore, with regard to each of the three neurologic outcome measures, (1) the effect of temperature did not significantly vary with temporary clip duration; (2) the effect of supplemental protective drug did not significantly vary with temporary clip duration; and (3) and the effect of supplemental protective drug did not significantly vary with temperature.

All Step 1 interaction terms were nonsignificant and, as a result, all interaction terms were sequentially removed from the models. As shown in table 6, the resulting Step 2 multivariate models indicate that neither intraoperative hypothermia ($P = 0.696$; OR = 0.927) nor supplemental protective drug ($P = 0.475$; OR = 1.155) was associated with 24-h neurologic status. Likewise, neither intraoperative hypothermia ($P = 0.696$; OR = 0.925) nor supplemental protective drug ($P = 0.926$; OR = 0.981) was associated with 3-month GOS score. Finally, neither intraoperative hypothermia ($P = 0.092$; OR = 1.532) nor supplemental protective drug ($P = 0.684$; OR = 0.901) was associated with 3-month Neuropsychological Composite Score. In Step 2 models, temporary clip duration greater than or equal to 20 min was associated with (1) less favorable 24-h neurologic outcome ($P = 0.003$; OR = 0.405) and (2) less favorable 3-month GOS score ($P = 0.010$; OR = 0.469). Reanalysis of the data excluding patients who had received etomidate as the supplemental protective drug (n = 20) did not meaningfully change any Step 1 or Step 2 results (data provided in Supplemental

Table 3. Postoperative Neurologic Morbidity and Outcomes

Variable	Temporary Clip Duration ≤10 min (n = 279)	11–19 min (n = 104)	≥20 min (n = 58)	*P* Value
Postoperative meningitis or ventriculitis, n (%)	7 (3)	5 (5)	7 (12)	0.008
Postoperative cerebral infarction, n (%)	74 (27)	27 (26)	26 (45)	0.019
Postoperative delayed ischemic neurologic deficit, n (%)	71 (25)	20 (19)	15 (26)	0.432
Good outcome (no neurologic deterioration) at 24 h, n (%)	161 (58)	62 (60)	21 (36)	0.007
Good outcome (Glasgow Outcome Scale = 1) at 3 mo, n (%)	186 (67)	64 (62)	28 (48)	0.031
Good outcome (no impairment on Neuropsychological Composite Score) at 3 mo, n (%)*	207 (80)	80 (81)	39 (76)	0.798
Mortality at 3 mo, n (%)	21 (8)	5 (5)	7 (12)	0.242

All *P* values are calculated using Fisher exact test.

* Patients who had died by 3 months did not have Neuropsychological Composite Score.

Digital Content 1, tables S-9 and S-10, respectively, http://links.lww.com/ALN/A561).

In Step 3, a forward stepwise model selection process tested 20 pre- and intraoperative variables for inclusion in the outcome models and for their effect on the associations between protective interventions, temporary clip duration, and outcomes. As summarized in table 6, with one possible exception, inclusion of covariates did not meaningfully change the results regarding the lack of association between hypothermia or supplemental protective drug and outcome. With covariate inclusion, Step 3 multivariate models still showed that neither hypothermia nor supplemental protective drug had any association with either 24-h neurologic status or 3-month GOS score. The one exception was that, in the Step 3 model of 3-month Neuropsychological Composite Score, hypothermia had a borderline association with more favorable outcome ($P = 0.043$, OR = 1.872). However, because no corrections were made for multiple comparisons, this finding could be a Type I error. We reasoned that if hypothermia truly resulted in better 3-month neuropsychologic outcome, this association should also be present with another neuropsychologic outcome measure. Accordingly, a Step 3 multivariate model was developed for the absence of abnormalities on any single neuropsychologic test. This alternative neuropsychologic outcome measure has been used in previous IHAST reports regarding neuropsychologic outcome.[11,23–26] By using this alternative measure, hypothermia did not have an association with 3-month neuropsychologic status; $P = 0.368$; OR = 1.218 (data provided in Supplemental Digital Content 1, table S-11, http://links.lww.com/ALN/A561). Therefore, we consider the borderline association between hypothermia and better Neuropsychological Composite Score to probably be a Type I error. In Step 3 models, despite the inclusion of covariates, temporary clip duration greater than or equal to 20 min remained associated with (1) less favorable 24-h neurologic outcome and (2) less favorable 3-month GOS score, although the strength of the association was less than in Step 2 models.

Twenty covariates were tested for inclusion in Step 3 models; seven satisfied inclusion criteria (table 6). Increasing age was associated with less favorable outcome with all outcome measures. Less favorable preoperative neurologic status, reflected in either best verbal response or NIH Stroke scale, and greater hemorrhage severity (Fisher scale) were associated with less favorable outcomes. Of the 10 intraoperative variables that were tested, greater blood loss and greater total surgery duration were associated with less favorable outcome. Greater intraoperative Pa_{O_2} was associated with better outcome at 24 h but not thereafter.

Discussion

Key Findings and Clinical Relevance

Our analysis indicates that neither mild systemic hypothermia nor supplemental protective drug had any meaningful association with early or late neurologic outcomes in patients undergoing temporary clipping. These results are consistent with the primary findings of the IHAST as a whole, wherein intraoperative hypothermia did not affect neurologic or neuropsychologic outcome. Our results also indicate that administration of supplemental pharmacologic agents during temporary clipping did not affect neurologic outcomes.

Hypothermia during Cerebral Aneurysm Surgery

IHAST was a prospective, randomized trial designed to prospectively assess the neurologic benefit of mild intraoperative systemic hypothermia (33°C) during intracranial aneurysm surgery. IHAST found that intraoperative hypothermia did not affect neurologic, functional[10] or neuropsychologic[11,27] outcomes. However, it is possible that not all IHAST patients experienced a significant intraoperative ischemic

Table 4. Unadjusted Primary Outcomes

Outcome	Temperature*	Supplemental Protective Drug*	Temporary Clip Duration ≤10 min (n = 279)	Temporary Clip Duration 11–19 min (n = 104)	Temporary Clip Duration ≥20 min (n = 58)	All Clip Durations†
Good Outcome (no neurologic deterioration) at 24 h after surgery	Normothermia	Supplemental protective drug	35/57 (61%)	17/26 (65%)	7/17 (41%)	59/100 (59%)
		No supplemental protective drug	58/95 (61%)	10/24 (42%)	4/14 (29%)	72/133 (54%)
		All normothermia patients	93/152 (61%)	27/50 (54%)	11/31 (35%)	131/233 (56%)
	Hypothermia	Supplemental protective drug	17/36 (47%)	20/29 (69%)	5/13 (39%)	42/78 (54%)
		No supplemental protective drug	51/91 (56%)	15/25 (60%)	5/14 (36%)	71/130 (55%)
		All hypothermia patients	68/127 (54%)	35/54 (65%)	10/27 (37%)	113/208 (54%)
Good Outcome (Glasgow Outcome Scale = 1) at 3 mo after surgery	Normothermia	Supplemental protective drug	38/57 (67%)	16/26 (62%)	11/17 (65%)	65/100 (65%)
		No supplemental protective drug	67/95 (71%)	12/24 (50%)	5/14 (36%)	84/133 (63%)
		All normothermia patients	105/152 (69%)	28/50 (56%)	16/31 (52%)	149/233 (64%)
	Hypothermia	Supplemental protective drug	22/36 (61%)	19/29 (66%)	4/13 (31%)	45/78 (58%)
		No supplemental protective drug	59/91 (65%)	17/25 (68%)	8/14 (57%)	84/130 (65%)
		All hypothermia patients	81/127 (64%)	36/54 (67%)	12/27 (44%)	129/208 (62%)
Good Outcome (no impairment on Neuropsychological Composite Score) at 3 mo after surgery‡	Normothermia	Supplemental protective drug	38/52 (73%)	19/26 (73%)	13/16 (81%)	79/94 (75%)
		No supplemental protective drug	69/88 (78%)	17/21 (81%)	8/11 (73%)	94/120 (78%)
		All normothermia patients	107/140 (76%)	36/47 (77%)	21/27 (78%)	164/214 (77%)
	Hypothermia	Supplemental protective drug	29/33 (88%)	25/29 (86%)	8/12 (67%)	62/74 (84%)
		No supplemental protective drug	71/85 (84%)	19/23 (83%)	10/12 (83%)	100/120 (83%)
		All hypothermia patients	100/118 (85%)	44/52 (85%)	18/24 (75%)	162/194 (84%)

In each cell, the numerator is the number of patients who had good outcome, the denominator is the total number of patients; the percentage refers to those who had good outcome.

* Patients in normothermia and hypothermia subgroups are subgrouped as those who received supplemental protective drug and those who did not. When the drug subgroups are combined, they are referred to as "All Patients." † When patients in all of the temporary clip duration subgroups are combined, they are referred to as "All Clip Durations." ‡ Patients who had died by 3 months (n = 33) did not have Neuropsychological Composite Scores.

event. Logically, only patients who experienced a substantive ischemic challenge during surgery could have any potential benefit from a protective intervention. Patients undergoing temporary clipping would seem to be the subgroup at greatest risk of an intraoperative ischemic event. Temporary clipping during aneurysm surgery is directly analogous to animal temporary focal ischemia models, wherein hypothermia has been repeatedly demonstrated to decrease infarction volume and improve neurobehavioral scores.[28] However, our analysis indicates that, even in this high-risk subgroup of IHAST patients, intraoperative hypothermia conferred no clinically demonstrable neurologic benefit.

In IHAST, hypothermia was of relatively brief duration. Systemic hypothermia was induced before temporary clipping and was maintained during the ischemic interval. Rewarming started only after final clip placement. Although

Table 5. Multivariate Models with Inclusion of Interaction Terms (Step 1)

Outcome	Variables	*P* Value (*df*)*
Good outcome (no neurologic deterioration) at 24 h after surgery	Temperature (hypothermia *vs.* normothermia [reference])	0.504 (1)
	Supplemental protective drug (drug *vs.* none [reference])	0.894 (1)
	Temporary clip duration (≥20 min, 11–19 min *vs.* ≤10 min [reference])	0.016 (2)
	Temperature—supplemental protective drug interaction term	0.292 (1)
	Temperature—temporary clip duration interaction term	0.189 (2)
	Supplemental protective drug—temporary clip duration interaction term	0.191 (2)
	Model c-statistic	*0.605*
Good outcome (Glasgow Outcome Scale = 1) at 3 mo after surgery	Temperature (hypothermia *vs.* normothermia [reference])	0.751 (1)
	Supplemental protective drug (drug *vs.* none [reference])	0.894 (1)
	Temporary clip duration (≥20 min, 11–19 min *vs.* ≤10 min [reference])	0.061 (2)
	Temperature—supplemental protective drug interaction term	0.246 (1)
	Temperature—temporary clip duration interaction term	0.253 (2)
	Supplemental protective drug—temporary clip duration interaction term	0.703 (2)
	Model c-statistic	*0.580*
Good outcome (no impairment on Neuropsychological Composite Score) at 3 mo after surgery	Temperature (hypothermia *vs.* normothermia [reference])	0.244 (1)
	Supplemental protective drug (drug *vs.* none [reference])	0.613 (1)
	Temporary clip duration (≥20 min, 11–19 min *vs.* ≤10 min [reference])	0.939 (2)
	Temperature—supplemental protective drug interaction term	0.537 (1)
	Temperature—temporary clip duration interaction term	0.575 (2)
	Supplemental protective drug—temporary clip duration interaction term	0.971 (2)
	Model c-statistic	*0.581*

* *P* values with more than 1 *df* represent omnibus *P* value for that variable.

still mildly hypothermic at the end of surgery (~34.5°C), patients randomized to hypothermia were rewarmed within 2 h after surgery. Animal temporary focal ischemia studies show moderate hypothermia limited to the ischemic interval and, in some studies for a brief (1–2 h) period thereafter, confers neurologic benefit when outcome assessments are made within the first few days.[29–37] However, with one exception,[38] animal temporary focal ischemia studies showing long-term (1–2 months) benefit with hypothermia have used extended periods of postischemic hypothermia—many hours or even days.[39–41] Accordingly, one might hypothesize that, in IHAST, the duration of hypothermia might have been sufficient to improve short-term outcomes but not long-term outcomes. Nevertheless, our results indicate no neurologic benefit with hypothermia, either 24 h after surgery or 3 months later.

In a rat temporary focal ischemia model, the protective effect of intraischemic hypothermia (33°C) was greater when followed by slow rewarming (2°C/h) than with rapid rewarming (~12°C/h).[37] Because rapid warming may decrease hypothermic protection, it has been suggested that the absence of benefit with hypothermia in IHAST was on this basis.[42] In IHAST, although rewarming began after final clip placement, it was sufficiently slow that core temperatures had increased by only approximately 1°C by the end of surgery, resulting in an initial rewarming rate of approximately 0.6°C/h. Two hours of postoperative rewarming were required before normothermia was reestablished, giving a subsequent rewarming rate of approximately 1°C/h. Therefore, IHAST rewarming rates were moderate and were 10-fold less than those shown in animal studies, to be associated with adverse effects.[37,43,44] We cannot rule out

Table 6. Multivariate Outcome Models

Outcome	Variables	Primary Variables Only (Step 2)*		Primary Variables with Covariates (Step 3)†	
		P Value (*df*)‡	Odds Ratio (95% CI)§	*P* Value (*df*)‡	Odds Ratio (95% CI)§
Good outcome (no neurologic deterioration) at 24 h after surgery	Temperature (hypothermia *vs.* normothermia [reference])	0.696 (1)	0.927 (0.632–1.358)	0.515 (1)	0.868 (0.565–1.331)
	Supplemental protective drug (drug *vs.* none [reference])	0.475 (1)	1.155 (0.777–1.717)	0.330 (1)	1.248 (0.799–1.951)
	Temporary clip duration	0.007 (2)		0.060 (2)	
	11–19 min *vs.* ≤10 min [reference]	0.815 (1)	1.057 (0.663–1.684)	0.833 (1)	1.058 (0.629–1.779)
	≥20 min *vs.* ≤10 min [reference]	0.003 (1)	0.405 (0.224–0.731)	0.024 (1)	0.464 (0.238–0.902)
	Model c-statistic	*0.566*		*0.720*‖	
Good outcome (Glasgow Outcome Scale = 1) at 3 mo after surgery	Temperature (hypothermia *vs.* normothermia [reference])	0.696 (1)	0.925 (0.625–1.368)	0.847 (1)	1.043 (0.678–1.606)
	Supplemental protective drug (drug *vs.* none [reference])	0.926 (1)	0.981 (0.654–1.471)	0.835 (1)	1.048 (0.674–1.631)
	Temporary clip duration	0.035 (2)		0.135 (2)	
	11–19 min *vs.* ≤10 min [reference]	0.376 (1)	0.807 (0.502–1.297)	0.757 (1)	0.920 (0.542–1.562)
	≥20 min *vs.* ≤10 min [reference]	0.010 (1)	0.469 (0.263–0.834)	0.046 (1)	0.527 (0.281–0.989)
	Model c-statistic	*0.570*		*0.696*#	
Good outcome (no impairment on Neuropsychological Composite Score) at 3 mo after surgery	Temperature (hypothermia *vs.* normothermia [reference])	0.092 (1)	1.532 (0.933–2.516)	0.043 (1)	1.872 (1.020–3.433)
	Supplemental protective drug (drug *vs.* none [reference])	0.684 (1)	0.901 (0.544–1.491)	0.623 (1)	1.161 (0.640–2.109)
	Temporary clip duration	0.831 (2)		0.436 (2)	
	11–19 min *vs.* ≤10 min [reference]	0.919 (1)	1.032 (0.566–1.881)	0.969 (1)	0.986 (0.478–2.031)
	≥20 min *vs.* ≤10 min [reference]	0.578 (1)	0.813 (0.393–1.683)	0.209 (1)	0.594 (0.263–1.340)
	Model c-statistic	*0.564*		*0.790***	

* Step 2 models include only the three variables of interest after stepwise removal of all nonsignificant interaction terms from Step 1 models (see Methods). † Step 3 models include the three variables of interest, with testing and adjustment for 20 covariates (see Methods). ‡ *P* values with >1 *df* represent omnibus *P* value for that variable. § A variable associated with an increased likelihood of a good outcome was considered to be "protective" and has an odds ratio >1. A variable associated with a decreased likelihood of a good outcome is detrimental and has an odds ratio <1. ‖ Other variables in the final model: age ($P = 0.007$; OR = 0.975), impaired preoperative best verbal score ($P = 0.002$; OR = 0.365), intraoperative blood loss ($P < 0.001$; OR = 0.999), and intraoperative Pa_{O_2} ($P = 0.003$; OR = 1.003). # Other variables in the final model: age ($P = 0.004$; OR=0.973), preoperative National Institutes of Health Stroke Scale score (*P* [3 *df*] < 0.001), and total surgery duration ($P = 0.011$; OR = 0.997). ** Other variables in the final model: age ($P = 0.011$; OR = 0.967), race ($P < 0.001$; OR = 7.978), preoperative Fisher score (*P* [3 *df*] = 0.017).

that slower rewarming rates in hypothermic patients might have resulted in better outcomes. However, slower rewarming would have required continuation of hypothermia for many hours into the postoperative period.

Most animal temporary focal ischemia studies have used infarction volume as an outcome measure. The primary advantage of this measure is its objectivity, and infarction volumes usually correlate with neurologic outcome. In contrast, most clinical studies of temporary clipping have used the diagnosis of cerebral infarction as an outcome measure. We decided not to use cerebral infarction as a primary outcome measure in our analysis. In IHAST, the diagnosis of postoperative cerebral infarction could be made at any time from surgery to 3 months after surgery. The diagnosis could be based on either clinical or radiologic criteria, but postoperative imaging was not required. Specifically, cranial imaging to document cerebral infarction at specified time points after surgery was not part of IHAST protocols, nor was there any attempt to calculate infarction volumes from images obtained as part of routine care. Because of (1) variability in the time of diagnosis of cerebral infarction and (2) variability in the diagnostic criteria (clinical or imaging), we decided not to use cerebral infarction as a primary outcome measure in this study. Nevertheless, for completeness, a Step 3 multivariate model was developed for postoperative cerebral infarction. Neither hypothermia ($P = 0.420$; OR = 1.205) nor supplemental protective drug ($P = 0.787$; OR = 0.938) had associations with postoperative cerebral infarction (data provided in Supplemental Digital Content 1, table S-12, http://links.lww.com/ALN/A561).

Pharmacologic Protection during Cerebral Aneurysm Surgery

In IHAST, supplemental protective drug administration was neither randomized nor standardized and was, instead, left to the discretion of the operative team. Accordingly, administration of these agents was subject to selection bias. For ex-

ample, teams might have elected to use these agents when operative conditions were less favorable. Indeed, our data indicate that supplemental protective drug was administered more often when temporary clip duration exceeded 10 min. Therefore, associations between supplemental protective drug and outcomes must be considered with this important limitation in mind.

Our analysis indicates that supplemental protective drug had no clinically detectable effect on outcome. Doses of supplemental thiopental used in this study (6–7 mg/kg) were less than those needed to induce and maintain electroencephalographic burst suppression in normothermic patients (15–20 mg/kg over 15 min, followed by 3 $mg \cdot kg^{-1} \cdot h^{-1}$ thereafter).[45] However, two recent rat temporary focal ischemia studies have shown that infarction volumes are equally decreased with high-dose (burst suppression) and low-dose (nonburst suppression) barbiturate regimens.[46,47] A Step 2 multivariate analysis limited to patients receiving thiopental (n = 157) found no association between thiopental dose and any of the three primary outcome measures (data provided in Supplemental Digital Content 1, table S-13, http://links.lww.com/ALN/A561). Therefore, the absence of a protective effect with supplemental protective drug cannot be readily ascribed to insufficient dosage.

Rat temporary focal ischemia studies that have demonstrated protective effects with intraischemic barbiturate administration have done so only under normothermic conditions.[46–50] In a recent study, barbiturate burst suppression during hypothermic ischemia did not provide greater protection beyond that observed with hypothermia alone.[50] In our analysis, we specifically tested for an interaction between supplemental protective drug and temperature. We found no significant interaction. In other words, there was no evidence that the effect of supplemental protective drug significantly differed between hypothermic and normothermic patients.

Rat temporary focal ischemia studies demonstrating protective effects with intraischemic barbiturate administration have done so only using short-term outcome assessments, either within the first few hours[49,50] or first few days[46,48,50] after ischemia. To our knowledge, there are no studies demonstrating a long-term (weeks to months) protective effect with barbiturates in temporary focal ischemia models when barbiturate administration has been limited to the peri-ischemic interval; this includes primate models of temporary focal ischemia.[51,52] In fact, the two most recent primate temporary focal ischemia studies report contradictory findings regarding the effect of barbiturates. In the study by Nehls *et al.*,[51] baboons receiving thiopental had lesser infarct volumes and better neurologic outcomes 7 days after temporary focal ischemia when compared with isoflurane controls. However, baboons receiving thiopental had greater arterial pressures and lesser blood glucose concentrations during ischemia than those receiving isoflurane. A subsequent study by Milde *et al.*,[52] in which arterial pressures were equivalent between thiopental and isoflurane groups, reported no differences in infarction volume or neurologic outcome 8 days after temporary focal ischemia. Therefore, it is possible that, as has been observed for other anesthetics,[53–55] barbiturates might only improve short-term outcomes, with neurologic benefits dissipating over time. Nevertheless, in IHAST, there was no significant benefit with supplemental protective drug 24 h after surgery. Similarly, at 3 months, there was no indication that supplemental protective drug affected outcome.

Etomidate was selected as the protective drug in a small minority of patients (n = 20). In the late 1980s, this drug was suggested as an alternative to barbiturates because it has a more clinically favorable hemodynamic and emergence profile.[56] However, subsequent animal studies,[49] including one from the original proponent,[57] have not shown etomidate to have significant protective effects. Nevertheless, using multivariate analysis (Step 1 and Step 2 models), the absence of effect with supplemental protective drug and the absence of drug-temperature interactions remained unchanged when patients who received etomidate were excluded.

An obvious limitation of this study is that administration of supplemental protective drug was not randomized, leading to variations in indications for therapy and dose of drug. However, the inclusion of covariates in Step 3 models did not affect the primary results—there was no association between supplemental protective drug and outcome. Until such time as a randomized controlled study of supplemental protective drug during temporary clipping is performed, our analysis indicates that clinicians should not expect these agents to improve neurologic outcomes.

Temporary Clip Duration and Outcome

Patients who had temporary clip durations greater than or equal to 20 min had less favorable outcomes. Therefore, one possible reason for the lack of effect with hypothermia and supplemental protective drug is simply because temporary clip durations less than 20 min did not constitute a clinically significant ischemic challenge. All patients received a volatile anesthetic before or during temporary clipping. Recently, volatile anesthetics have been shown to have long-term protective effects (as compared with the awake state) in the setting of mild ischemic insults.[58,59] IHAST patients were also relatively hyperoxic, which may increase ischemic tolerance,[60–62] and both normotension and normoglycemia were generally well maintained. Collectively, these conditions may have increased brain ischemic tolerance.

Patients who underwent temporary clipping for greater than or equal to 20 min (n = 58) constituted only 13% of the patients who underwent temporary clipping. It might seem logical to conclude that less favorable outcomes in this subgroup were the direct result of an ischemic event caused by prolonged temporary clipping. Although this may be so, it is apparent that these patients came to the operating room with a less favorable neurologic condition, as indicated by less favorable preoperative verbal scores and NIH Stroke Scale scores. In addition, greater intraoperative complexity in these patients is indicated by less favorable aneurysm exposure,

greater total surgery duration and number of applied clips, more frequent aneurysm wrapping, and by trends toward a greater frequency of aneurysm leak or rupture, greater blood loss, and supplemental protective drug dose. Either singly or in combination, these pre- and intraoperative factors would likely contribute to less favorable outcomes. Therefore, although prolonged temporary clip duration may directly cause ischemic injury, ischemic injury may also be related to, or result from, the associated less favorable operative conditions. Nevertheless, in the Step 3 models, wherein preoperative neurologic status and intraoperative conditions were considered, temporary clip duration greater than or equal to 20 min remained associated with less favorable outcome at 24 h and 3 months (GOS). It seems that the few patients who require temporary clipping for more than or equal to 20 min are at increased risk of perioperative ischemic injury, independent of other unfavorable conditions. Nevertheless, outcomes were not significantly affected by temperature or supplemental protective drug in this subgroup of patients. Reanalysis of 3-month GOS scores in this subgroup, with GOS scores dichotomized as GOS 1 and 2 *versus* GOS 3–5, did not change conclusions regarding the lack of benefit with hypothermia or supplemental protective drug (data provided in Supplemental Digital Content 1, table S-14, http://links.lww.com/ALN/A561).

Limitations

In any study that does not detect an outcome difference with an intervention, one must address the question of a Type II error—that the sample size was not sufficient to detect the treatment effect. With regard to 3-month GOS, with a rate of good outcome of 64% in normothermic patients (n = 233), our population of hypothermic patients (n = 208) was sufficiently large to detect an absolute increase of 13% (relative increase of 20%) in good outcomes ($\alpha = 0.05$, $\beta = 0.20$, two-sided test). Likewise, this study had sufficient power to detect an absolute increase of 13% (relative increase of 20%) in 3-month good outcome with supplemental protective drug.

Our Step 1 logistic analyses indicated that the effect of supplemental protective drug did not significantly differ between hypothermic and normothermic patients. This result was largely determined by the largest subgroup of patients who underwent temporary clipping—patients with temporary clip durations less than or equal to 10 min (n = 279). Inspection of table 4 indicates that, in patients who had temporary clip durations less than or equal to 10 min, supplemental protective drug had no discernable effect on outcome under either hypothermic or normothermic conditions. However, inspection of table 4 suggests that supplemental protective drug might favorably affect outcome in normothermic patients with temporary clip durations exceeding 10 min. If limited to normothermic patients with temporary clip durations more than 10 min, with a 3-month GOS = 1 of 45% (17 of 38) in patients who did not receive supplemental protective drug and a 3-month GOS = 1 of 63% (27 of 43) in patients who received supplemental protective drug, a total sample size of 262 patients (131 per group) would be required to have sufficient statistical power to establish the favorable effect of supplemental protective drug under these conditions ($\alpha = 0.05$, $\beta = 0.20$, two-sided test). Therefore, although it is possible that hypothermia and/or supplemental protective drug may improve outcome in some patients under some conditions, the size of the treatment effect is too small to be detected in a population of 441 patients undergoing temporary clipping—less than a 15–20% absolute increase in favorable outcomes. Any study to detect such small treatment effects in patients undergoing temporary clipping would require a very large multicenter effort, equal to or exceeding that of IHAST.

IHAST data collection procedures did not record the indications for temporary clipping. Although temporary clipping is most often used electively, it may also be used as a rescue method to control bleeding from aneurysm rupture.[9,63,64] Inspection of table 2 suggests that patients who had long temporary clip durations had a greater frequency and/or severity of aneurysm rupture as evidenced by greater blood loss, greater transfusion, greater total surgery duration, greater number of clips, and greater use of aneurysm wrapping. Intraoperative aneurysm rupture is associated with less favorable outcome.[4,64,65] Therefore, it is possible that the association with long temporary clip durations and less favorable outcomes may be due, at least in part, to a greater frequency and/or severity of aneurysm rupture.

Another limitation of IHAST data collection is that temporary clip duration was recorded as total time, regardless of whether temporary clipping took place as a single continuous period or as a series of brief intermittent occlusions. Some studies suggest that, for an equal amount of total ischemia time, intermittent occlusion may result in a lesser likelihood of neurologic injury.[6] Because of IHAST data collection procedures, the IHAST database cannot address this question.

Conclusion

In 441 patients undergoing temporary clipping during cerebral aneurysm surgery, neither intraoperative hypothermia nor supplemental protective drug had any clinically demonstrable effect on short- or long-term neurologic outcomes. There was no significant interaction between temperature and supplemental protective drug, and the absence of protective effects did not vary as a function of temporary clip duration.

References

1. Jabre A, Symon L: Temporary vascular occlusion during aneurysm surgery. Surg Neurol 1987; 27:47–63
2. Charbel FT, Ausman JI, Diaz FG, Malik GM, Dujovny M, Sanders J: Temporary clipping in aneurysm surgery: Technique and results. Surg Neurol 1991; 36:83–90
3. Samson D, Batjer HH, Bowman G, Mootz L, Krippner WJ, Meyer YJ, Allen BC: A clinical study of the parameters and

effects of temporary arterial occlusion in the management of intracranial aneurysms. Neurosurgery 1994; 34:22–9
4. Ogilvy CS, Carter BS, Kaplan S, Rich C, Crowell RM: Temporary vessel occlusion for aneurysm surgery: Risk factors for stroke in patients protected by induced hypothermia and hypertension and intravenous mannitol administration. J Neurosurg 1996; 84:785–91
5. Taylor CL, Selman WR, Kiefer SP, Ratcheson RA: Temporary vessel occlusion during intracranial aneurysm repair. Neurosurgery 1996; 39:893–906
6. Lavine SD, Masri LS, Levy ML, Giannotta SL: Temporary occlusion of the middle cerebral artery in intracranial aneurysm surgery: Time limitation and advantage of brain protection. J Neurosurg 1997; 87:817–24
7. Araki Y, Andoh H, Yamada M, Nakatani K, Andoh T, Sakai N: Postoperative hyperperfusion caused by temporary clipping. Neurol Med Chir (Tokyo) 1999; 39:901–7
8. Hütter B, Kreitschmann-Andermahr I, Gilsbach JM: Health-related quality of life after aneurysmal subarachnoid hemorrhage: Impacts of bleeding severity, computerized tomography findings, surgery, vasospasm, and neurological grade. J Neurosurg 2001; 94:241–51
9. Ferch R, Pasqualin A, Pinna G, Chioffi F, Bricolo A: Temporary arterial occlusion in the repair of ruptured intracranial aneurysms: An analysis for risk factors for stroke. J Neurosurg 2002; 97:836–42
10. Todd MM, Hindman BJ, Clarke WR, Torner JC; IHAST Investigators: Mild intraoperative hypothermia during surgery for intracranial aneurysm. N Engl J Med 2005; 352: 135–45
11. Anderson SW, Todd MM, Hindman BJ, Clarke WR, Torner JC, Tranel D, Yoo B, Weeks J, Manzel KW, Samra S: Effects of intraoperative hypothermia on neuropsychological outcomes after intracranial aneurysm surgery. Ann Neurol 2006; 60:518–27
12. Drake CG: Report of World Federation of Neurological Surgeons Committee on a universal subarachnoid hemorrhage grading scale. J Neurosurg 1988; 68:985–6
13. Fisher CM, Kistler JP, Davis JM: Relation of cerebral vasospasm to subarachnoid hemorrhage visualized by computerized tomographic scanning. Neurosurgery 1980; 6:1–9
14. Wityk RJ, Pessin MS, Kaplan RF, Caplan LR: Serial assessment of acute stroke using the NIH Stroke Scale. Stroke 1994; 25:362–5
15. Jennett B, Bond M: Assessment of outcome after severe brain damage: A practical scale. Lancet 1975; 1:480–4
16. The Publications Committee for the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) Investigators: Low molecular weight heparinoid, ORG 10172 (danaproid), and outcome after acute ischemic stroke: A randomized controlled trial. JAMA 1998; 279:1256–72
17. Sivan AB: The Benton Visual Retention Test, 5th edition. San Antonio, The Psychological, 1992
18. Benton AL, Hamsher KD: The Multilingual Aphasia Examination. Iowa City, AJA Associates Inc., 1994
19. Lezak M: Neuropsychological Assessment, 3rd edition. New York, Oxford University Press, 1995, pp 475–80
20. Heaton RK, Grant I, Matthews CG: Comprehensive Norms for an Expanded Halstead-Reitan Battery: Demographic Corrections, Research Findings and Clinical Applications. Odessa, Psychological Assessment Resources, 1991
21. Valtysson J, Hillered L, Andine P, Hagberg H, Persson L: Neuropathological endpoints in experimental stroke pharmacotherapy: The importance of both early and late evaluation. Acta Neurochir (Wien) 1994; 129:58–63
22. Kawaguchi M, Kimbro JR, Drummond JC, Cole DJ, Kelly PJ, Patel PM: Isoflurane delays but does not prevent cerebral infarction in rats subjected to focal ischemia. ANESTHESIOLOGY 2000; 92:1335–42
23. Todd MM, Hindman BJ, Clarke WR, Torner JC, Weeks JB, Bayman EO, Shi Q, Spofford CS; IHAST Investigators: Perioperative fever and outcome in surgical patients with aneurysmal subarachnoid hemorrhage. Neurosurgery 2009; 64:897–908
24. McGregor DG, Lanier WL, Pasternack JJ, Rusy DA, Hogan K, Samra S, Hindman B, Todd MM, Schroeder DR, Bayman EO, Clarke W, Torner J, Weeks J; IHAST Investigators: Effect of nitrous oxide on neurological and neuropsychological function following intracranial aneurysm surgery. ANESTHESIOLOGY 2008; 108:568–79
25. Pasternak JJ, McGregor DG, Schroeder DR, Lanier WL, Shi Q, Hindman BJ, Clarke WR, Torner JC, Weeks J, Todd MM; IHAST Investigators: Hyperglycemia in patients undergoing cerebral aneurysm surgery: Its association with long-term gross neurologic and neuropsychological function. Mayo Clin Proc 2008; 83:406–17
26. Pasternack JJ, McGregor DG, Lanier WL, Schroeder DR, Rusy DA, Hindman B, Clarke WR, Torner JC, Weeks J, Todd MM; IHAST Investigators: Effect of nitrous oxide use on long term neurologic and neuropsychological outcome in patients who received temporary proximal artery occlusion during cerebral aneurysm clipping surgery. ANESTHESIOLOGY 2009; 110:563–73
27. Samra SK, Giordani B, Cavency AF, Clarke WR, Scott PA, Anderson S, Thompson BG, Todd MM; CFAAST Investigators: Recovery of cognitive function after surgery for aneurysmal subarachnoid hemorrhage. Stroke 2007; 38:1864–72
28. van der Worp HB, Sena ES, Donnan GA, Howells DW, Macleod MR: Hypothermia in animal models of acute ischaemic stroke: A systematic review and meta-analysis (review). Brain 2007; 130:3063–74
29. Chen H, Chopp M, Zhang ZG, Garcia JH: The effect of hypothermia on transient middle cerebral artery occlusion in the rat. J Cereb Blood Flow Metab 1992; 12:621–8
30. Ridenour TR, Warner DS, Todd MM, McAllister AC: Mild hypothermia reduces infarct size resulting from temporary but not permanent focal ischemia in rats. Stroke 1992; 23:733–8
31. Xue D, Huang ZG, Smith KE, Buchan AM: Immediate or delayed mild hypothermia prevents focal cerebral infarction. Brain Res 1992; 587:66–72
32. Goto Y, Kassell NF, Hiramatsu K, Soleau SW, Lee KS: Effects of intraischemic hypothermia on cerebral damage in a model of reversible focal ischemia. Neurosurgery 1993; 32:980–5
33. Karibe H, Chen J, Zarow GJ, Graham SH, Weinstein PR: Delayed induction of mild hypothermia to reduce infarct volume after temporary middle cerebral artery occlusion in rats. J Neurosurg 1994; 80:112–9
34. Markarian GZ, Lee JH, Stein DJ, Hong SC: Mild hypothermia: Therapeutic window after experimental cerebral ischemia. Neurosurgery 1996; 38:542–51
35. Maier CM, Ahern KV, Cheng ML, Lee JE, Yenari MA, Steinberg GK: Optimal depth and duration of mild hypothermia in a focal model of transient cerebral ischemia: Effects on neurologic outcome, infarct size, apoptosis, and inflammation. Stroke 1998; 29:2171–80
36. Huh PW, Belavey L, Zhao W, Koch S, Busto R, Ginsberg MD: Comparative neuroprotective efficacy of prolonged moderate intraischemic and postischemic hypothermia in focal cerebral ischemia. J Neurosurg 2000; 92:91–9
37. Berger C, Xia F, Köhrmann M, Schwab S: Hypothermia in acute stroke—slow versus fast rewarming: An experimental study in rats. Exp Neurol 2007; 204:131–7
38. Maier CM, Sun GH, Kunis D, Yenari MA, Steinberg GK: Delayed induction and long-term effects of mild hypothermia in a focal model of transient cerebral ischemia: Neurological outcome and infarct size. J Neurosurg 2001; 94:90–6
39. Yanamoto H, Nagata I, Nakahara I, Tohnai N, Zhang Z, Kikuchi H: Combination of intraischemic and postischemic hypothermia provides potent and persistent neuroprotection against temporary focal ischemia in rats. Stroke 1999; 30:2720–6
40. Corbett D, Mamilton M, Colbourne F: Persistent neuroprotection with prolonged postischemic hypothermia in adult

rats subjected to transient middle cerebral artery occlusion. Exp Neurol 2000; 163:200–6
41. Colbourne F, Corbett D, Zhao Z, Yang J, Buchan AM: Prolonged but delayed postischemic hypothermia: A long-term outcome study in the rat middle cerebral artery occlusion model. J Cereb Blood Flow Metab 2000; 20: 1702–8
42. Polderman KH: Induced hypothermia and fever control for prevention and treatment of neurological injuries (review). Lancet 2008; 371:1955–69
43. Nakamura T, Miyamoto O, Yamagami S-I, Hayashida Y, Itano T, Nagao S: Influence of rewarming conditions after hypothermia in gerbils with transient forebrain ischemia. J Neurosurg 1999; 91:114–20
44. Suehiro E, Ueda Y, Wei EP, Kontos HA, Povlishock JT: Posttraumatic hypothermia followed by slow rewarming protects the cerebral microcirculation. J Neurotrauma 2003; 20:381–90
45. Todd MM, Drummond JC, Sang UH: The hemodynamic consequences of high-dose thiopental anesthesia. Anesth Analg 1985; 64:681–7
46. Warner DS, Takaoka S, Wu B, Ludwig PS, Pearlstein RD, Brinkhous AD, Dexter F: Electroencephalographic burst suppression is not required to elicit maximal neuroprotection from pentobarbital in a rat model of focal cerebral ischemia. ANESTHESIOLOGY 1996; 84:1475–84
47. Schmid-Elsaesser R, Schröder M, Zausinger S, Hungerhuber E, Baethmann A, Reulen HJ: EEG burst suppression is not necessary for maximum barbiturate protection in transient focal cerebral ischemia in the rat. J Neurol Sci 1999; 162:14–9
48. Warner DS, Zhou J, Ramani R, Todd MM: Reversible focal ischemia in the rat: Effects of halothane, isoflurane, and methohexital anesthesia. J Cereb Blood Flow Metab 1991; 11:794–802
49. Drummond JC, Cole DJ, Patel PM, Reynolds LW: Focal cerebral ischemia during anesthesia with etomidate, isoflurane, or thiopental: A comparison of the extent of cerebral injury. Neurosurgery 1995; 37:742–9
50. Westermaier T, Zausinger S, Baethmann A, Steiger HJ, Schmid-Elsaesser R: No additional neuroprotection provided by barbiturate-induced burst suppression under mild hypothermic conditions in rats subjected to reversible focal ischemia. J Neurosurg 2000; 93:835–44
51. Nehls DG, Todd MM, Spetzler RF, Drummond JC, Thompson RA, Johnson PC, Mendenhall SE, Barstow CA, Carmichael PG, Young DM, Fifield MS, Jones CP: A comparison of the cerebral protective effects of isoflurane and barbiturates during temporary focal ischemia in primates. ANESTHESIOLOGY 1987; 66:453–64
52. Milde LN, Milde JH, Lanier WL, Michenfelder JD: Comparison of the effects of isoflurane and thiopental on neurologic outcome and neuropathology after temporary focal cerebral ischemia in primates. ANESTHESIOLOGY 1988; 69: 905–13
53. Kawaguchi M, Drummond JC, Cole DJ, Kelly PJ, Spurlock MP, Patel PM: Effect of isoflurane on neuronal apoptosis in rats subjected to focal cerebral ischemia. Anesth Analg 2004; 98:798–805
54. Elsersy H, Sheng H, Lynch JR, Moldovan M, Pearlstein RD, Warner DS: Effects of isoflurane *versus* fentanyl-nitrous oxide anesthesia on long-term outcome from severe forebrain ischemia in the rat. ANESTHESIOLOGY 2004; 100: 1160–6
55. Bayon NA, Gelb AW, Jian Z, Wilson JX, Urquhart BL, Cechetto DF: Propofol neuroprotection in cerebral ischemia and its effects on low-molecular-weight antioxidants and skilled motor tasks. ANESTHESIOLOGY 2004; 100:1151–9
56. Batjer HH, Frankfurt AI, Purdy PD, Smith SS, Samson DS: Use of etomidate, temporary arterial occlusion, and intraoperative angiography in surgical treatment of large and giant cerebral aneurysms. J Neurosurg 1988; 68:234–40
57. Guo J, White JA, Batjer HH: Limited protective effects of etomidate during brainstem ischemia in dogs. J Neurosurg 1995; 82:278–83
58. Pape M, Engelhard K, Eberspacher E, Hollweck R, Kellermann K, Zintner S, Hutzler P, Werner C: The long-term effect of sevoflurane on neuronal cell damage and expression of apoptotic factors after cerebral ischemia and reperfusion in rats. Anesth Analg 2006; 103:173–9
59. Sakai H, Sheng H, Yates RB, Ishida K, Pearlstein RD, Warner DS: Isoflurane provides long-term protection against focal cerebral ischemia in the rat. ANESTHESIOLOGY 2007; 106:92–9
60. Liu S, Shi H, Liu W, Furuichi T, Timmins GS, Liu KJ: Interstitial pO2 in ischemic penumbra and core are differentially affected following transient focal cerebral ischemia in rats. J Cereb Blood Flow Metab 2004; 24:343–9
61. Shin HK, Dunn AK, Jones PB, Boas DA, Lo EH, Moskowitz MA, Ayata C: Normobaric hyperoxia improves cerebral blood flow and oxygenation, and inhibits peri-infarct depolarizations in experimental focal ischemia. Brain 2007; 130:1631–42
62. Singhal AB, Dijkhuizen RM, Rosen BR, Lo EH: Normobaric hyperoxia reduced MRI diffusion abnormalities and infarct size in experimental stroke. Neurology 2008; 58:945–52
63. Fridriksson S, Säveland H, Jakobsson KE, Edner G, Zygmunt S, Brandt L, Hillman J: Intraoperative complications in aneurysm surgery: A prospective national study. J Neurosurg 2002; 96:515–22
64. Woertgen C, Rothoerl RD, Albert R, Schebesch KM, Ullrich OW: Effect of temporary clipping during aneurysm surgery. Neurol Res 2008; 30:542–6
65. Elijovich L, Higashida RT, Lawton MT, Duckwiler G, Giannotta S, Johnston C; CARAT Investigators: Predictors and outcomes of intraprocedural rupture in patients treated for ruptured intracranial aneurysms: The CARAT study. Stroke 2008; 39:1501–6

Appendix

The members of Intraoperative Hypothermia for Aneurysm Surgery Trial were as follows:

University of Iowa Steering Committee: M. Todd, B. Hindman, W. Clarke, K. Chaloner, J. Torner, P. Davis, M. Howard, D. Tranel, S. Anderson; Clinical Coordinating Center: M. Todd, B. Hindman, J. Weeks, L. Moss, J. Winn; Data Management Center: W. Clarke, K. Chaloner, M. Wichman, R. Peters, M. Hansen, D. Anderson, J. Lang, B. Yoo; Physician Safety Monitor: H. Adams; Project Advisory Committee: G. Clifton (University of Texas, Houston), A. Gelb (University of California, San Francisco), C. Loftus (Temple University, Philadelphia), A. Schubert (Cleveland Clinic, Cleveland); Physician Protocol Monitor: D. Warner (Duke University, Durham, North Carolina); Data and Safety Monitoring Board: W. Young, Chair (University of California, San Francisco), R. Frankowski (University of Texas Health Science Center at Houston School of Public Health, Houston), K. Kieburtz (University of Rochester School of Medicine and Dentistry, Rochester, New York), D. Prough, University of Texas Medical Branch, Galveston), L. Sternau (Mt. Sinai Medical Center, Miami); National Institutes of Health, National Institute of Neurologic Disease and Stroke, Bethesda, Maryland: J. Marler, C. Moy, B. Radziszewska.

Participating Centers (the number of randomized patients at each center is listed in parentheses) were as follows:

Addenbrooke's Hospital, Cambridge, United Kingdom (93): B. Matta, P. Kirkpatrick, D. Chatfield, C. Skilbeck, R. Kirollos, F. Rasulo, K. English, C. Duffy, K. Pedersen, N. Scurrah, R. Burnstein, A. Prabhu, C. Salmond, A. Blackwell, J. Birrell, S. Jackson; University of Virginia Health System, Charlottesville (86): N. Kassell, T. Pajewski, H. Fraley, A. Morris, T. Alden, M. Shaffrey, D. Bogdonoff, M. Durieux, Z. Zuo, K. Littlewood, E. Nemergut, R. Bedford, D. Stone, P. Balestrieri, J. Mason, G. Henry, P. Ting, J. Shafer, T. Blount, L. Kim, A. James, E. Farace, L. Clark, M. Irons, T. Sasaki, K. Webb; Auckland City Hospital, Auckland, New Zealand (69): T. Short, E. Mee, J. Ormrod, J. Jane, T. Alden, P. Heppner, S. Olson, D. Ellegala, C. Lind, J. Sheehan, M. Woodfield, A. Law, M. Harrison, P. Davies, D. Campbell, N. Robertson, R. Fry, D. Sage, S. Laurent, C. Bradfield, K. Pedersen, K. Smith, Y. Young, C. Chambers, B. Hodkinson, J. Biddulph, L. Jensen, J. Ogden, Z. Thayer, F. Lee, S. Crump, J. Quaedackers, A. Wray, V. Roelfsema; Sozialmedizinisches Zentrum Ost–Donauspital, Vienna (58): R. Greif, G. Kleinpeter, C. Lothaller, E. Knosp, W. Pfisterer, R. Schatzer, C. Salem, W. Kutalek, E. Tuerkkan, L. Koller, T. Weber, A. Buchmann, C. Merhaut, M. Graf, B. Rapf; Harborview Medical Center, Seattle (58): A. Lam, D. Newell, P. Tanzi, L. Lee, K. Domino, M. Vavilala, J. Bramhall, M. Souter, G. Britz, H. Winn, H. Bybee; St. Vincent's Public Hospital, Melbourne, Australia (57): T. Costello, M. Murphy, K. Harris, C. Thien, D. Nye, T. Han, P. McNeill, B. O'Brien, J. Cormack, A. Wyss, R. Grauer, R. Popovic, S. Jones, R. Deam, G. Heard, R. Watson, L. Evered, F. Bardenhagen, C. Meade, J. Haartsen, J. Kruger, M. Wilson; University of Iowa Health Care, Iowa City (56): M. Maktabi, V. Traynelis, A. McAllister, P. Leonard, B. Hindman, J. Brian, F. Mensink, R. From, D. Papworth, P. Schmid, D. Dehring, M. Howard, P. Hitchon, J. VanGilder, J. Weeks, L. Moss, K. Manzel, S. Anderson, R. Tack, D. Taggard, P. Lennarson, M. Menhusen; University of Western Ontario, London, Ontario, Canada (53): A. Gelb, S. Lownie, R. Craen, T. Novick, G. Ferguson, N. Duggal, J. Findlay, W. Ng, D. Cowie, N. Badner, I. Herrick, H. Smith, G. Heard, R. Peterson, J. Howell, L. Lindsey, L. Carriere, M. von Lewinski, B. Schaefer, D. Bisnaire, P. Doyle-Pettypiece, M. McTaggart; Keck School of Medicine at University of Southern California, Los Angeles (51): S. Giannotta, V. Zelman, E. Thomson, E. Babayan, C. McCleary, D. Fishback; University of Michigan Medical Center, Ann Arbor (41): S. Samra, B. Thompson, W. Chandler, J. Mcgillicuddy, K. Tremper, C. Turner, P. Smythe, E. Dy, S. Pai, V. Portman, J. Palmisano, D. Auer, M. Quigley, B. Giordani, A. Freymuth, P. Scott, R. Silbergleit, S. Hickenbottom; University of California San Francisco, San Francisco (39): L. Litt, M. Lawton, L. Hannegan, D. Gupta, P. Bickler, B. Dodson, P. Talke, I. Rampil, B. Chen, P. Wright, J. Mitchell, S. Ryan, J. Walker, N. Quinnine, C. Applebury; Alfred Hospital, Melbourne, Australia (35): P. Myles, J. Rosenfeld, J. Hunt, S. Wallace, P. D'Urso, C. Thien, J. McMahon, S. Wadanamby, K. Siu, G. Malham, J. Laidlaw, S. Salerno, S. Alatakis, H. Madder, S. Cairo, A. Konstantatos, J. Smart, D. Lindholm, D. Bain, H. Machlin, J. Moloney, M. Buckland, A. Silvers, G. Downey, A. Molnar, M. Langley, D. McIlroy, D. Daly, P. Bennett, L. Forlano, R. Testa, W. Burnett, F. Johnson, M. Angliss, H. Fletcher; Toronto Western Hospital, University Health Network, Toronto (32): P. Manninen, M. Wallace, K. Lukitto, M. Tymianski, P. Porter, F. Gentili, H. El-Beheiry, M. Mosa, P. Mak, M. Balki, S. Shaikh, R. Sawyer, K. Quader, R. Chelliah, P. Berklayd, N. Merah, G. Ghazali, M. McAndrews, J. Ridgley, O. Odukoya, S. Yantha; Wake Forest University Baptist Medical Center, Winston-Salem, North Carolina (31): J. Wilson, P. Petrozza, C. Miller, K. O'Brien, C. Tong, M. Olympio, J. Reynolds, D. Colonna, S. Glazier, S. Nobles, D. Hill, H. Hulbert, W. Jenkins; Mayo Clinic College of Medicine, Rochester, Minnesota (28): W. Lanier, D. Piepgras, R. Wilson, F. Meyer, J. Atkinson, M. Link, M. Weglinski, K. Berge, D. McGregor, M. Trenerry, G. Smith, J. Walkes, M. Felmlee-Devine; West Fälische Wilhelms-Universitat Muenster, Muenster, Germany (27): H. Van Aken, C. Greiner, H. Freise, H. Brors, K. Hahnenkamp, N. Monteiro de Oliveira, C. Schul, D. Moskopp, J. Woelfer, C. Hoenemann, H. Gramke, H. Bone, I. Gibmeier, S. Wirtz, H. Lohmann, J. Freyhoff, B. Bauer; University of Wisconsin Clinical Science Center, Madison (26): K. Hogan, R. Dempsey, D. Rusy, B. Badie, B. Iskandar, D. Resnick, P. Deshmukh, J. Fitzpatrick, F. Sasse, T. Broderick, K. Willmann, L. Connery, J. Kish, C. Weasler, N. Page, B. Hermann, J. Jones, D. Dulli, H. Stanko, M. Geraghty, R. Elbe; Montreal Neurologic Hospital, Montreal (24): F. Salevsky, R. Leblanc, N. Lapointe, H. Macgregor, D. Sinclair, D. Sirhan, M. Maleki, M. Abou-Madi, D. Chartrand, M. Angle, D. Milovan, Y. Painchaud; Johns Hopkins Medical Institutions, Baltimore (23): M. Mirski, R. Tamargo, S. Rice, A. Olivi, D. Kim, D. Rigamonti, N. Naff, M. Hemstreet, L. Berkow, P. Chery, J. Ulatowski, L. Moore, T. Cunningham, N. McBee, T. Hartman, J. Heidler, A. Hillis, E. Tuffiash, C. Chase, A. Kane, D. Greene-Chandos, M. Torbey, W. Ziai, K. Lane, A. Bhardwaj, N. Subhas; Cleveland Clinic Foundation, Cleveland (20) A. Schubert, M. Mayberg, M. Beven, P. Rasmussen, H. Woo, S. Bhatia, Z. Ebrahim, M. Lotto, F. Vasarhelyi, J. Munis, K. Graves, J. Woletz, G. Chelune, S. Samples, J. Evans, D. Blair, A. Abou-Chebl, F. Shutway, D. Manke, C. Beven; New York Presbyterian Hospital–Weill Medical College of Cornell University, New York (15): P. Fogarty-Mack, P. Stieg, R. Eliazo, P. Li, H. Riina, C. Lien, L. Ravdin, J. Wang, Y. Kuo; Stanford University Medical Center, Palo Alto, California (15): R. Jaffe, G. Steinberg, D. Luu, S. Chang, R. Giffard, H. Lemmens, R. Morgan, A. Mathur, M. Angst, A. Meyer, H. Yi, P. Karzmark, T. Bell-Stephens, M. Marcellus; Plymouth Hospitals National Health Service Trust, Plymouth, United Kingdom (14): J. Sneyd, L. Pobereskin, S. Salsbury, P. Whitfield, R. Sawyer, A. Dashfield,

R. Struthers, P. Davies, A. Rushton, V. Petty, S. Harding, E. Richardson; University of Pittsburgh Medical Center, Pittsburgh (11): H. Yonas, F. Gyulai, L. Kirby, A. Kassam, N. Bircher, L. Meng, J. Krugh, G. Seever, R. Hendrickson, J. Gebel; Austin Health, Melbourne, Australia (10): D. Cowie, G. Fabinyi, S. Poustie, G. Davis, A. Drnda, D. Chandrasekara, J. Sturm, T. Phan, A. Shelton, M. Clausen, S. Micallef; Methodist University Hospital, Memphis, Tennessee (8): A. Sills, F. Steinman, P. Sutton, J. Sanders, D. Van Alstine, D. Leggett, E. Cunningham, W. Hamm, B. Frankel, J. Sorenson, L. Atkins, A. Redmond, S. Dalrymple; University of Alabama at Birmingham, Birmingham (7): S. Black, W. Fisher, C. Hall, D. Wilhite, T. Moore II, P. Blanton, Z. Sha; University of Texas Houston Health Science Center, Houston (7): P. Szmuk, D. Kim, A. Ashtari, C. Hagberg, M. Matuszczak, A. Shahen, O. Moise, D. Novy, R. Govindaraj; University of Colorado Health Science Center, Denver (4): L. Jameson, R. Breeze, I. Awad, R. Mattison, T. Anderson, L. Salvia, M. Mosier; University of Oklahoma Health Science Center, Oklahoma City (3): C. Loftus, J. Smith, W. Lilley, B. White, M. Lenaerts.