**Introduction**

Elevated intracranial pressure that occurs at the time of cerebral aneurysm rupture can lead to inadequate cerebral blood flow, which may mimic the brain injury cascade that occurs after cardiac arrest. Insights from clinical trials in cardiac arrest may provide direction for future early brain injury research after subarachnoid hemorrhage (SAH). Methods. A search of PubMed from 1980 to 2012 and clinicaltrials.gov was conducted to identify published and ongoing randomized clinical trials in aneurysmal SAH and cardiac arrest patients. Only English, adult, human studies with primary or secondary mortality or neurological outcomes were included. Results. A total of 142 trials (82 SAH, 60 cardiac arrest) met the review criteria (103 published, 39 ongoing). The majority of both published and ongoing SAH trials focus on delayed secondary insults after SAH (70%), while 100% of cardiac arrest trials tested interventions within the first few hours of ictus. No SAH trials addressing treatment of early brain injury were identified. Twenty-nine percent of SAH and 13% of cardiac arrest trials showed outcome benefit, though there is no overlap mechanistically. Conclusions. Clinical trials in SAH assessing acute brain injury are warranted and successful interventions identified by the cardiac arrest literature may be reasonable targets of the study.

1. Introduction

For decades, research efforts in subarachnoid hemorrhage (SAH) have focused on vasospasm and delayed ischemic neurological deficits. However, brain injury at the time of aneurysm rupture is a significant predictor of functional outcome. Indeed, poor admission neurological status (Hunt-Hess or World Federation of Neurological Surgeons Score), which reflects acute brain injury, is a larger contributor to death or severe disability than delayed cerebral ischemia [1, 2]. However, the mechanism of early brain injury after aneurysm rupture remains elusive and no current therapies are available.

One possible mechanism of acute injury was described in a small case series of 6 patients with observed recurrent aneurysm rupture either during transcranial Doppler (TCD) or during craniotomy with open skull but intact dura. The investigators report a spike in intracranial pressure (ICP) that developed over 1 minute and then declined over several minutes. This abrupt increase in ICP approached levels near mean arterial pressure and led to a concomitant drop in cerebral blood flow resulting in circulatory arrest, as documented by TCD [61]. This study examined aneurysm rebleeding and does not provide direct evidence that intracranial circulatory arrest occurs with de novo aneurysm rupture. However, inadequate cerebral blood flow is frequently evidenced clinically by the transient loss of consciousness that occurs at SAH ictus. This mechanism of global transient circulatory arrest has been described in animal models of SAH at the time of initial hemorrhage [62, 63] and mimics the anoxic/hypoxic ischemic mechanism incurred by cardiac arrest.

In this paper, published and ongoing clinical trials in cardiac arrest are compared to those in aneurysmal SAH to identify overlapping or complementary approaches to treatment as well as new avenues for potential research.

2. Methods

A search of PubMed was conducted in 11/2012 to identify randomized, controlled trials of aneurysmal SAH and cardiac arrest. Only human studies of adults (≥18 years of age), which
| Trial name | Study design | Treatment group | Control group | Outcome measure | Results | Reference |
|------------|--------------|-----------------|---------------|----------------|---------|-----------|
| Calcium channel blockers—nimodipine |
| Cerebral Arterial Spasm—a controlled Trial of Nimodipine in Patients with Subarachnoid Hemorrhage | Randomized, placebo-controlled, double-blind, multicenter prospective study of Hunt Hess grade I-II SAH patients | Nimodipine 0.7 mg/kg PO bolus, then 0.35 mg/kg q 4 × 21 days. Starting within 96 h of SAH (N = 58) | Placebo (N = 63) | Primary outcome: neurological deficit from arterial spasm and severity of neurologic deficit at 21 days | Nimodipine significantly reduced death or severe deficits from spasm at 21 days (2% versus 13% with placebo, P = 0.03) | Allen et al., NEJM 1983 [3] |
| Nimodipine treatment in poor-grade aneurysm patients. Results of a multicenter double-blind placebo-controlled trial | Randomized, multicenter, double-blind, placebo-controlled trial | Nimodipine 90 mg PO q 4h × 21d (N = 91) | Placebo (N = 97) | Primary outcome: 3-month GOS Secondary outcomes: delayed ischemic deficits, angiographic vasospasm | Better 3-month GOS in treatment group (29% versus 9% of treatment group, P < 0.001). Significantly less delayed cerebral ischemia in treatment group, no difference in angiographic vasospasm | Petruk et al., J Neurosurg 1988 [4] |
| Controlled study of nimodipine in aneurysm patients treated early after subarachnoid hemorrhage | Randomized, double-blind, placebo-controlled trial of all Hunt-Hess grades within 96 hours of SAH | Nimodipine 60 mg q 4h PO × 21 days + Nimodipine 200 mcg IV intraoperatively into basal cistern (N = 38) | Placebo (N = 37) | Primary outcome: mortality, cerebral blood flow measured by Xenon CT Secondary outcomes: 3-month intellectual or neurological deficit | Mortality was lower in the nimodipine group (4% versus 24% with placebo, P < 0.05). Nimodipine did not significantly increase cerebral blood flow | Mee et al., Neurosurgery 1988 [5] |
| Effect of oral nimodipine on cerebral infarction and outcome after subarachnoid hemorrhage: British aneurysm nimodipine trial | Randomized, double-blind, placebo-controlled, multicenter trial within 96 h of SAH | Nimodipine 60 mg q 4 PO × 21d (N = 276) | Placebo (N = 278) | Primary outcome: 3-month cerebral infarction Secondary outcome: 3-month GOS | Significantly less cerebral infarction in the nimodipine group (22% compared to 33% in placebo, P = 0.014). Poor GOS outcomes significantly reduced in nimodipine group at 3-months | Pickard et al., BMJ 1989 [6] |
| Early aneurysm surgery and preventive Therapy with intravenously administered nimodipine: A multicenter, double-blind, dose-comparison study | Randomized, double-blind, dose-comparison, multicenter study | Nimodipine 2 mg/h IV for 9–15 days (N = 101) | Nimodipine 3 mg/h IV for 9–15 days (N = 103) | Primary outcome: delayed neurological deficits, adverse drug reactions | No difference in delayed neurological deficits between the two groups | Gilksb et al., Neurosurgery 1990 [7] |
| Trial name                                                      | Study design                                      | Treatment group                          | Control group                           | Outcome measure                                      | Results                                                                                       | Reference                        |
|---------------------------------------------------------------|--------------------------------------------------|------------------------------------------|-----------------------------------------|-----------------------------------------------------|-----------------------------------------------------------------------------------------------|----------------------------------|
| Long-term effects of nimodipine on cerebral infarcts and outcome after aneurysmal subarachnoid hemorrhage and surgery | Randomized, double-blind, placebo-controlled of Hunt-Hess I–III SAH patients | Nimodipine IV 0.5 mcg/kg/min × 7–10 days followed by 60 mg q 4 h PO × 21 days total (N = 104) | Placebo (N = 109) | Primary outcome: delayed ischemic deterioration and CT infarcts Secondary outcomes: GOS at 1–3 years | Significantly fewer deaths caused by delayed cerebral ischemia in nimodipine group (P = 0.01) and fewer cerebral infarcts on CT (P = 0.05). No differences in 1–3 year GOS or CT scan | Ohman et al., J Neurosurg 1991 [8] |
| A randomized outcome study of enteral versus intravenous nimodipine in 171 patients after acute aneurysmal subarachnoid hemorrhage | Randomized, single-center study                  | Nimodipine 2 mg/h IV × 10 days then changed to PO × 6 d (N = 87) | Nimodipine 60 mg PO q 4 × 16 days (N = 84) | Primary outcome: delayed ischemic neurological deficit Secondary outcomes: 12 month GOS, mRS, Karnofsky, MRI infarcts, HRQoL | No difference in delayed ischemic neurological deficits (20% in enteral versus 16% in IV group, P = 0.61), no difference in 12-month clinical outcomes | Soppi et al., World Neurosurgery 2012 [9] |
| Calcium channel blockers—nicardipine                          |                                                  | Nicardipine IV 0.15 mg/kg/h (N = 449)  | Placebo (N = 457) | Primary outcome: 3-month GOS Secondary outcomes: angiographic vasospasm, TCD vasospasm, mortality, disability from vasospasm, symptomatic vasospasm, CT infarction, NIHSS | No difference in 3-month GOS. Less symptomatic vasospasm in treatment group (32% versus 46% in placebo group, P < 0.001) and less angiographic vasospasm in treatment group (33% versus 51% of placebo, P < 0.01) and less TCD vasospasm (23% versus 49% of placebo, P < 0.001) | Hakel et al., J Neurosurg 1993 [10, 11] |
| A randomized trial of two doses of nicardipine in aneurysmal subarachnoid hemorrhage. A report of the cooperative aneurysm study | Randomized, double-blind, placebo-controlled, multicenter study | Nicardipine IV 0.15 mg/kg/h × 14 days (N = 184) | Nicardipine IV 0.075 mg/kg/h × 14 days (N = 181) | Primary outcome: symptomatic vasospasm, adverse drug events Secondary outcomes: 3-month GOS and NIHSS, mortality, disability due to vasospasm, CT infarction | No difference in symptomatic vasospasm or 3-month outcome. More adverse effects in high-dose nicardipine group | Hakel et al., J Neurosurg 1994 [12] |
| Effect of nicardipine prolonged-release implants on cerebral vasospasm and clinical outcome after severe aneurysmal subarachnoid hemorrhage. A prospective, randomized, double-blind phase IIa Study | Randomized, prospective double-blind phase IIa study in clipped SAH patients | Nicardipine prolonged-release implants (10 × 4 mg prolonged release rod shaped polymers) placed in basal cisterns (N = 16) | Control basal cisterns opened and washed out (N = 16) | Primary outcome: angiographic vasospasm Secondary outcome: delayed ischemic lesion on HCT, 1-year mRS and NIHSS | Angiographic vasospasm significantly reduced in treatment group (7% versus 73% in controls, P < 0.05). No significant difference in CT infarct. Decreased mortality in treatment group (6% versus 38% in control group, P = 0.042) and better 1-year mRS and NIHSS (P = 0.0001) | Barth et al., Stroke 2007 [13] |
| Trial name                                                                 | Study design                                      | Treatment group | Control group | Outcome measure                                                                 | Results                                                                 | Reference                  |
|---------------------------------------------------------------------------|--------------------------------------------------|-----------------|---------------|---------------------------------------------------------------------------------|-------------------------------------------------------------------------|----------------------------|
| **Antifibrinolytics**                                                    |                                                  |                 |               |                                                                                |                                                                         |                            |
| Antifibrinolysis with tranexamic acid in aneurysmal subarachnoid hemorrhage: A consecutive controlled clinical trial | Randomized, placebo-controlled, study           | Tranexamic acid 1 g q 4 h IV × 1 week then 1 g q 6 h IV × 1 week then 1.5 g q 6 h PO × 1 week (N = 30) | Placebo (N = 29) | Primary outcome: recurrent hemorrhage diagnosed by LP, HCT, echoencephalogram or autopsy; Secondary outcome: angiographic vasospasm, delayed cerebral ischemia, death | Tranexamic acid protected against rebleeding during the first 2 weeks of treatment but also resulted in cerebral ischemic complications | Fodstad et al., Neurosurgery 1981 [14] |
| Comparative clinical trial of epsilon amino-caproic acid and tranexamic acid in the prevention of early recurrence of subarachnoid hemorrhage | Randomized trial                                 | Epsilon amino-caproic acid 6 g q 6 h IV continued until surgery or discharge (N = 90) | Tranexamic acid 1 g q 6 h IV continued until surgery or discharge (N = 61) | Primary outcome: recurrent hemorrhage diagnosed clinically by HCT, LP, or autopsy; Secondary outcome: delayed ischemic deficit diagnosed by clinical deterioration, angiographic vasospasm, and infarct on HCT | Rebleeding occurred in 8% of aminocaproic-acid-treated patients and 10% of tranexamic acid treated patients. Delayed ischemic deficits occurred in 7% of aminocaproic acid patients and 5% of tranexamic acid patients. Mortality was 11% in each group. P = NS for all outcomes | Chowdhary and Sayed, JNNP 1981 [15] |
| Antifibrinolytic treatment in subarachnoid hemorrhage                     | Randomized, double-blind, placebo-controlled, multicenter study | Tranexamic acid 1 g q 4 h IV × 1 week then 1 g q 6 h IV × 3 weeks (N = 241) | Placebo (N = 238) | Primary outcome: 3-month GOS Secondary outcome: neurological deterioration, rebleeding, infarction, hydrocephalus, edema, epilepsy | No difference in 3-month GOS. Significant decrease in rebleeding from 24% in control group to 9% in treatment group (P < 0.001), but with concurrent increase in ischemic complications (24% in treatment group versus 15% in placebo, P < 0.01). No difference in 3-month GOS | Vermeulen et al., NEJM 1984 [16] |
| Antifibrinolytic treatment in subarachnoid hemorrhage: a randomized placebo-controlled trial (STAR) | Prospective, double-blind, placebo-controlled, multicenter, randomized trial within 96 hours of SAH onset in whom aneurysm repair was delayed beyond 48 hours | Tranexamic acid 1 g IV q 4 h × 1 week then 1.5 g PO q 6 h × 2 weeks (N = 229) | Placebo (N = 233) | Primary outcome: 3-month GOS Secondary outcomes: rebleeding, delayed cerebral ischemia, hydrocephalus, postoperative ischemia | No difference in 3-month GOS. Significant decrease in rebleeding from 33% in placebo group to 19% in treatment group. No difference in delayed cerebral ischemia, hydrocephalus, or postoperative ischemia | Roos, Neurology 2000 [17] |
Table 1: Continued.

| Trial name | Study design | Treatment group | Control group | Outcome measure | Results | Reference |
|------------|--------------|-----------------|---------------|-----------------|---------|-----------|
| Immediate administration of tranexamic acid and reduced incidence of early rebleeding after aneurysmal subarachnoid hemorrhage: a prospective randomized study | Randomized, placebo-controlled trial | Tranexamic acid 1g IV bolus, then 1g IV q 6 hours until aneurysm repair or 72 hours post ictus. \(N=254\) | Placebo \(N=251\) | Rebleeding outcome: Rebleeding by HCT | Treatment group had reduced rebleeding rate of 2.4% compared to 10.8% in the placebo group \(P<0.01\). More favorable outcome in the treatment group (74.8% compared to 70.5% in the control group, \(P=NS\)). No increased risk of ischemia | Hillman et al., J Neurosurg 2002 [18] |

**Neuroprotectives drugs**

| Trial name | Study design | Treatment group | Control group | Outcome measure | Results | Reference |
|------------|--------------|-----------------|---------------|-----------------|---------|-----------|
| A double-blind clinical evaluation of the effect of nizofenone on delayed ischemic neurological deficits following aneurysmal rupture | Randomized, placebo controlled trial | Nizofenone for 5–10 days \(N=42\) | Placebo \(N=48\) | Neurological exam at 1-month and discharge | No difference in delayed ischemic events between treatment groups. Among patients with vasospasm, those who received nizofenone had better one-month functional outcomes \(P<0.05\) | Suito et al., Neurol Res 1983 [19] |
| Nizofenone administration in the acute stage following subarachnoid hemorrhage. Results of a multicenter controlled double-blind clinical study | Randomized, double-blind, placebo-controlled, multicenter study of Hunt Hess grade I–IV | Nizofenone 5 mg \(\times 2\) weeks \(N=102\) | Placebo \(N=106\) | Neurological exam at 1-month and discharge | Significantly improved one-month or discharge functional outcome in treatment group compared to placebo \(P<0.05\). No difference in mortality | Ohta et al., J Neurosurg 1986 [20] |
| Effect of a free radical scavenger, edaravone, in the treatment of patients with aneurysmal subarachnoid hemorrhage | Randomized, controlled, single-center study | Edaravone 30 mg IV BID \(\times \) 14 days \(N=49\) | Control (usual treatment) \(N=42\) | Neurological exam at 1-month and discharge | No difference in delayed ischemic neurological deficits between treatment and control groups. Less cerebral infarction in treatment group (0% versus 66%, \(P=0.028\)). Poor outcome caused by vasospasm 0% in treatment group and 71% in control group \(P=0.046\) | Munakata et al., Neurosurgery 2009 [21] |
| Eicosapentaenoic Acid Cerebral Vasospasm Therapy Study (EVAS) | Randomized, controlled, open label, multicenter, efficacy study of surgically clipped SAH patients | Eicosapentaenoic acid (omega 3 fatty acid) 900 mg TID \(\times \) 30 days \(N=81\) | Control (usual treatment) \(N=81\) | Neurological exam at 1-month and discharge | Symptomatic vasospasm occurred significantly less in the treatment group (15% versus 30% in controls, \(P=0.022\)) as did infarction from vasospasm (7% versus 21% in controls, \(P=0.012\)) | Yoneda et al., World Neurosurg 2012 [22] |
### Table 1: Continued.

| Trial name                                                                 | Study design                          | Treatment group                          | Control group                  | Outcome measure                                                                 | Results                                                                                       | Reference                                                                                     |
|---------------------------------------------------------------------------|---------------------------------------|------------------------------------------|--------------------------------|---------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|
| Safety and efficacy of NA-1 in patients with iatrogenic stroke after endovascular aneurysm repair (ENACT): a phase 2, randomized, double-blind, placebo-controlled trial | Randomized, double-blind, placebo-controlled study of ruptured (WFNS 1–3) and unruptured aneurysms undergoing endovascular repair | NA-1 2.6 mg/kg infusion over 10 minutes (N = 92) | Placebo (N = 93) | Primary outcome: safety, number and volume of ischemic strokes on MRI DWI and FLAIR 12–96 hours after infusion Secondary outcome: 30-day mRS, NIHSS, neurocognitive outcome | No difference in MRI lesion volume, but fewer ischemic lesions in NA-1 group compared to placebo (P = 0.012). In the SAH subgroup (20% of cohort) their MRI number and ischemic volume was significantly less in the treatment group. No difference in 30 day NIHSS or mRS between groups | Hill et al., Lancet Neurol 2012 [23] |

#### Statins

| Simvastatin reduces vasospasm After aneurysmal subarachnoid hemorrhage: results of a pilot randomized clinical trial | Randomized, placebo-controlled pilot trial | Simvastatin 80 mg qd for 14 days (N = 19) | Placebo (N = 20) | Primary outcome: delayed ischemic neurological deficit confirmed by TCD or angiography. Secondary outcomes: liver transaminases, CK, von Willebrand factor, S100 | Vasospasm occurred in 26% of treatment group compared to 60% of placebo group (P < 0.05). No differences in transaminitis or myositis. VWF and S100 were significantly lower in the treatment group (P < 0.05). TCD vasospasm severe vasospasm were reduced in the treatment group (P = 0.006 and P = 0.044, resp.). Duration of impaired autoregulation shortened in treatment group (P < 0.01). Vasospasm-related delayed ischemic deficits was reduced (P < 0.001) and mortality was reduced (P = 0.037) | Lynch et al., Stroke 2005 [24] |

| Effects of acute treatment with pravastatin on cerebral vasospasm, autoregulation, and delayed Ischemic deficits after aneurysmal subarachnoid hemorrhage. A phase II randomized placebo-controlled trial | Randomized, placebo-controlled, phase II Trial | Pravastatin 40 mg PO qd x 14 d (N = 40) | Placebo (N = 40) | Primary outcome: incidence, severity and duration of vasospasm on TCD, duration of impaired autoregulation measured by transient hyperemic response on TCD Secondary outcome: vasospasm-related delayed ischemic deficits, disability at discharge | Primary outcome: death and drug morbidity (elevated CK, transaminases) Secondary outcomes: TCD, angiographic or clinical vasospasm, vasospasm-related infarcts, clinical outcomes at discharge, cardiac, and infectious morbidities | Tseng et al., Stroke 2005 [25] |

| A randomized, double-blind, placebo-controlled pilot study of simvastatin in aneurysmal subarachnoid hemorrhage | Randomized, double-blind, placebo-controlled pilot study | Simvastatin 80 mg qd in statin naive Fisher 3 SAH until discharge or 21 days (N = 19) | Placebo (N = 20) | Mortality in 0% treatment group and 15% placebo group. Angiographically confirmed vasospasm in 26% treatment group and 25% placebo group. Vasospasm infarcts in 11% treatment group and 25% placebo group. All differences P = NS | Mortality in 0% treatment group and 15% placebo group. Angiographically confirmed vasospasm in 26% treatment group and 25% placebo group. Vasospasm infarcts in 11% treatment group and 25% placebo group. All differences P = NS | Chou et al., Stroke 2008 [26] |
| Trial name                                                                 | Study design                                                                 | Treatment group                                                                 | Control group      | Outcome measure                                                                 | Results                                                                                                                                                                                                 | Reference |
|---------------------------------------------------------------------------|------------------------------------------------------------------------------|--------------------------------------------------------------------------------|-------------------|----------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| Simvastatin for patients with aneurysmal subarachnoid hemorrhage: a double-blind, placebo-controlled randomized trial | Double-blind placebo-controlled randomized trial (N = 16)                  | Simvastatin 80 mg PO × 15 days (N = 16)                                        | Placebo (N = 16)   | Primary outcome: 3-month dead, dependent or independent. Secondary outcomes: neurological deficit, rebleeding, confirmed rebleeding, delayed ischemic deterioration, hydrocephalus, extracranial complications. | Acute surgery patients were more often independent at 3-months (92% versus 79% in the late timing group and 80% in the early surgery group versus 73% in the late surgery group (P < 0.01). Mortality was 6% in the early surgery group versus 13% in the late surgery group (P = NS). | Ohman and Heiskanen, J Neurosurg 1989 [28] |
| Aneurysm repair: Timing of operation for ruptured supratentorial aneurysms: a prospective randomized study of Hunt Hess grade I–III SAH patients | Randomized, prospective study of Hunt Hess grade I–III SAH patients          | Acute surgery (day 0–3 after SAH) (N = 71)                                     | Intermediate surgery (day 4–7 after SAH) (N = 70) | Primary outcome: 1-year mortality. Secondary outcomes: 1-year survival, quality of life at 1-year (EuroQol), frequency of epilepsy, cost effectiveness, neuropsychological outcomes. | Endovascular treatment by detachable platinum coils (N = 1073) more beneficial 1-year survival (ARR 7.4%). Early survival advantage of coiling maintained up to 7 years (P < 0.001). Lower risk of epilepsy in coiled group but higher late rebleeding risk in coiled group. | Molyneux et al., Lancet 2005 [30] |
| International subarachnoid aneurysm trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with an aneurysm judged technically suitable for either clipping or coiling: a randomised comparison of effect on survival, dependency, seizures, effect on subgroups, and aneurysm occlusion | Randomized, unblinded trial of SAH patients with an aneurysm judged technically suitable for either clipping or coiling: a randomised comparison of effect on survival, dependency, seizures, effect on subgroups, and aneurysm occlusion | Surgical clipping (N = 1070)                                                   | Endovascular treatment by detachable platinum coils (N = 1073)                             | Primary outcome: 1-year dead or dependent. Secondary outcomes: 1-year survival, quality of life at 1-year (EuroQol), frequency of epilepsy, cost effectiveness, neuropsychological outcomes. | Surgical clipping (N = 1070) more beneficial 1-year survival (ARR 7.4%). Early survival advantage of coiling maintained up to 7 years (P < 0.001). Lower risk of epilepsy in coiled group but higher late rebleeding risk in coiled group. | Molyneux et al., Lancet 2005 [30] |
| International subarachnoid aneurysm trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with an aneurysm judged technically suitable for either clipping or coiling: a randomised comparison of effect on survival, dependency, seizures, effect on subgroups, and aneurysm occlusion | Randomized, unblinded trial of SAH patients with an aneurysm judged technically suitable for either clipping or coiling: a randomised comparison of effect on survival, dependency, seizures, effect on subgroups, and aneurysm occlusion | Surgical clipping (N = 1070)                                                   | Endovascular treatment by detachable platinum coils (N = 1073)                             | Primary outcome: 1-year dead or dependent. Secondary outcomes: 1-year survival, quality of life at 1-year (EuroQol), frequency of epilepsy, cost effectiveness, neuropsychological outcomes. | Surgical clipping (N = 1070) more beneficial 1-year survival (ARR 7.4%). Early survival advantage of coiling maintained up to 7 years (P < 0.001). Lower risk of epilepsy in coiled group but higher late rebleeding risk in coiled group. | Molyneux et al., Lancet 2005 [30] |
### Table 1: Continued.

| Trial name                                                                 | Study design                                      | Treatment group                      | Control group                   | Outcome measure                                      | Results                                                                 | Reference                     |
|---------------------------------------------------------------------------|---------------------------------------------------|--------------------------------------|----------------------------------|------------------------------------------------------|-------------------------------------------------------------------------|--------------------------------|
| The barrow ruptured aneurysm trial                                        | Randomized, open-label, prospective, single-center study | Surgical clipping (N = 238)         | Endovascular coiling (N = 233)   | Primary outcome: 1-year mRS > 2                      | Poor outcome in 33.7% of clipped and 23.2% of coiled patients (P = 0.02) | McDougall et al., J Neurosurg 2012 [31] |
| Lipid peroxidation inhibitor                                               | Double-blind, randomized, vehicle-controlled study in men and women with aneurysmal SAH | Tirilazad 0.6 mg/kg/ (N = 257)       | Placebo containing citrate vehicle (N = 253) | Primary outcome: Symptomatic vasospasm Secondary outcome: 3-month GOS, NIHSS, infarct volume on head CT | The subgroup 6 mg/kg treatment arm had reduced mortality (P = NS) and better 3-month GOS (P = NS) compared to placebo. Less symptomatic vasospasm in 6 mg/kg group, but not significant. Men showed more benefit than women. No significant improvement with lower dosing groups | Kassell et al., J Neurosurg 1996 [32] |
| A randomized, double-blind, vehicle-controlled trial of tirilazad mesylate in patients with aneurysmal subarachnoid hemorrhage: a cooperative study in North America | Double-blind, randomized, vehicle-controlled study in men and women with aneurysmal SAH | Tirilazad 2 mg/kg/d (N = 298)       | Placebo containing citrate vehicle (N = 300) | Primary outcome: mortality at 76 days Secondary outcome: 3-month GOS and NIHSS, infarct volume on head CT symptomatic vasospasm, incidence, and severity of angiographic vasospasm | No difference in mortality, favorable GOS outcome, or employment between groups. No differences in symptomatic or angiographic vasospasm | Haley et al., J Neurosurg 1997 [33] |
| Double-blind, randomized, vehicle-controlled study of high-dose tirilazad mesylate in women with aneurysmal subarachnoid hemorrhage. Part I a cooperative study in Europe, Australia, New Zealand, and South Africa | Double-blind, randomized, vehicle-controlled study in women with aneurysmal SAH | Tirilazad mesylate 15 mg/kg/d IV hours for 11 days (N = 405) | Placebo containing citrate vehicle (N = 414) | Primary outcome: 91-day mortality Secondary outcome: 3-month GOS, clinical vasospasm, use of hypervolemic hypertensive therapy, neurological worsening from vasospasm, cerebral infarction, use of angioplasty, safety endpoints | Mortality rates and 3-month GOS not different between groups. Lower symptomatic vasospasm in tirilazad group (24.8% versus 33.7% in placebo group, P = 0.005). Cerebral infarction 8% in treatment group versus 13% in placebo group (P < 0.04) | Lanzino et al., J Neurosurg 1999 [34] |
| Double-blind, randomized, vehicle-controlled study of high-dose tirilazad mesylate in women with aneurysmal subarachnoid hemorrhage. Part II a cooperative study in North America | Double-blind, randomized, vehicle-controlled study in women with aneurysmal SAH | Tirilazad mesylate 15 mg/kg/d IV up to 11 days (N = 410) | Placebo containing citrate vehicle (N = 413) | Primary outcome: mortality at 91 days in WFNS grade IV-V patients Secondary outcomes: 3 month GOS or clinical vasospasm 1–14 days from dosing, use of hypervolemic hypertensive therapy, neurological worsening from vasospasm, cerebral infarction, use of angioplasty, safety endpoints | No differences in mortality when analyzing the entire population. No difference in GOS, symptomatic vasospasm, vasospasm severity. In WFNS grades IV-V, lower mortality in treatment group (24.6% versus 43.4% in placebo, P = 0.016). In WFNS I–III improved GOS in placebo group (83.3% versus 76.7% in treatment group, P = 0.04) | Lanzino and Kassell, J Neurosurg 1999 [35] |
| Trial name                                                                 | Study design                                                                 | Treatment group                                                                 | Control group                                                                 | Outcome measure                                                                 | Results                                                                 | Reference                                                                 |
|---------------------------------------------------------------------------|------------------------------------------------------------------------------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------|---------------------------------------------------------------------------|
| Prevention of delayed ischemic deficits after aneurysmal subarachnoid hem    | Prospective, controlled trial of Fisher III clipped SAH patients              | rTPA 10 mg IV intracisternal immediately following aneurysm clipping ± 5–10 mg IV TPA intraventricularly in patients with IVH (N = 52) | No TPA instillation (N = 68)                                                                 | Primary outcome: clinical delayed ischemic deficits attributed to vasospasm | Significantly less transient and permanent delayed ischemic deficits and better ischemic deficits in rTPA group | Seifert et al., Acta Neurochir 1994 [36]                                         |
| hemorrhage by intrathecal bolus injection of tissue plasminogen activator (rTPA) |                                                                              |                                                                                  |                                                                                  | Secondary outcome: 3-month GOS                                                                 |                                                                         |                                                                           |
| A randomized trial of intraoperative, intracisternal tissue plasminogen activ | Randomized, double-blinded, placebo-controlled, multicenter study            | rTPA 10 mg intracisternal at the time of aneurysm clipping (N = 51)               | Placebo vehicle (N = 49)                                                                 | Primary outcome: angiographic vasospasm                                         | No difference in angiographic vasospasm, vasospasm treatment, TCD velocities, mortality, or 3-month GOS | Findlay, Neurosurgery 1995 [37]                                                   |
| for the prevention of vasospasm                                           |                                                                              |                                                                                  |                                                                                  | Secondary outcome: mortality, 3-month GOS, symptomatic vasospasm, clot clearance on CT, TCD velocities, use of HHH on angioplasty to treat vasospasm |                                                                         |                                                                           |
| Efficacy of low-dose tissue-plasminogen activator intracisternal administration for the prevention of cerebral vasospasm after subarachnoid hemorrhage | Randomized, controlled trial                                                | Intermittent Tisokinase 960,000 IU via cisternal drain  (N = 20)                 | Control (standard treatment) (N = 20)                                                   | Primary outcome: clearance of subarachnoid clots by HCT                     | Subarachnoid clot by HCT and delayed cerebral ischemia were significantly less in the treatment groups compared to control (P < 0.05). The intermittently treated group had better neurological outcomes than the control group (P < 0.05) | Yamamoto et al., World Neurosurgery 2010 [38]                                      |
| Dipyridamole and postoperative ischemic deficits in aneurysmal subarachnoid hemorrhage | Randomized, placebo-controlled, single-blind controlled trial              | Dipyridamole 100 mg PO qd or 10 mg/day IV × 3-months (N = 336)                    | Placebo (N = 314)                                                                      | Primary outcome: 3-month GOS                                                   | No differences in 3-month GOS or delayed neurological deterioration       | Shaw et al., J Neurosurg 1985 [39]                                              |
|                                                                               |                                                                              |                                                                                  |                                                                                  | Secondary outcome: neurological deterioration following aneurysm repair         |                                                                         |                                                                           |
| Randomized controlled trial of acetylsalicylic Acid in aneurysmal subarachnoid hemorrhage: the MASH study | Randomized controlled pilot study; factorial design (magnesium versus placebo, ASA versus placebo, separated a priori) | Aspirin 100 mg PR qd × 14 days within 12 hours of aneurysm occlusion. (N = 87) | Placebo (N = 74)                                                                      | Primary outcome: delayed ischemic neurological deficits within 3-months of SAH consisting of HCT infarcts plus clinical decline | No difference in delayed ischemic events, CT infarction, or 3-month outcomes | Van den Bergh, Stroke 2006 [40]                                                 |
### Table 1: Continued.

| Trial name                                                                 | Study design                        | Treatment group                      | Control group                  | Outcome measure                                      | Results                                                                 | Reference                        |
|---------------------------------------------------------------------------|-------------------------------------|--------------------------------------|--------------------------------|------------------------------------------------------|------------------------------------------------------------------------|----------------------------------|
| Cilostazol improves outcome after subarachnoid hemorrhage: a preliminary  | Randomized, single-blind, prospective, multicenter study | Cilostazol 100 mg PO BID (N = 49)     | Control (usual care) (N = 51) | Primary outcome: symptomatic vasospasm and cerebral infarction, mRS | No difference in symptomatic vasospasm or cerebral infarction. mRS at discharge better in treatment group (1.5 versus 2.6 in controls, *P* = 0.041) | Suzuki et al., Cerebrovasc Dis 2011 [41] |
| Effect of fludrocortisone acetate in patients with subarachnoid hemorrhage | Randomized, placebo controlled, multicenter trial | Fludrocortisone 400 mcg/day BID × 12 days PO or IV (N = 46) | Placebo (N = 45) | Secondary outcome: delayed cerebral ischemia within 28 days and 28-day GOS | Treatment reduced negative sodium balance (*P* = 0.014) but did not affect plasma volume. No significant difference in cerebral ischemia (22% versus 31% in controls, *P* = 0.349). Similar outcome in each group | Hasan et al., Stroke 1989 [42] |
| A randomized controlled trial of hydrocortisone against hyponatremia in patients with aneurysmal subarachnoid hemorrhage | Randomized, placebo-controlled study | Hydrocortisone 300 mg q 6h × 10d then taper over 4d (N = 35) | Placebo (N = 36) | Secondary outcome: 30-day mRS, symptomatic vasospasm | Less sodium excretion and urine volume in treatment group (*P* = 0.04). No significant differences in vasospasm or mRS | Katayama et al., Stroke 2007 [43] |
| Randomized, double-blind, placebo-controlled, pilot trial of high-dose methylprednisolone in aneurysmal subarachnoid hemorrhage | Randomized, double-blind, placebo-controlled, single center study | Methylprednisolone 16 mg/kg IV qd × 3 days (N = 49) | Placebo (N = 46) | Secondary Outcomes: 1 year GOS, functional outcome scale, and severity of delayed ischemic deficits | No significant difference in symptomatic vasospasm or infarct on HCT. No difference in 1-year GOS or delayed ischemic deficits at 3-months. Poor outcome by functional outcome scale was reduced in treatment group (*P* = 0.02) | Gomis et al., J Neurosurg 2010 [44] |
| Acute systemic erythropoietin therapy to reduce delayed ischemic deficits following aneurysmal subarachnoid hemorrhage: a phase II randomized, double-blind, placebo-controlled trial | Phase II randomized, double-blind, placebo-controlled trial | Erythropoietin IV (30,000 u) every 48 h for a total of 90,000 U (N = 40) | Placebo (N = 40) | Primary outcome: incidence, duration and severity of TCD vasospasm; duration of impaired autoregulation by TCD Secondary outcome: incidence of delayed ischemic deficits, mRS, GOS, and NIHSS at discharge and 6-months | No differences in incidence of TCD vasospasm or adverse events. Treatment group had less severe TCD vasospasm (*P* = −0.037), reduced delayed ischemic deficits/delayed cerebral infarcts (*P* = 0.001), and shortened duration of impaired autoregulation (*P* < 0.001) and more favorable discharge outcome (*P* = 0.039) | Tseng et al., J Neurosurg 2009 [45] |
| Trial name                                                                 | Study design                                                                 | Treatment group                                                                 | Control group                                                                 | Outcome measure                                                                 | Results                                                                                                                                                                                                 | Reference                                                                 |
|---------------------------------------------------------------------------|-------------------------------------------------------------------------------|---------------------------------------------------------------------------------|--------------------------------------------------------------------------------|---------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------|
| Prospective, randomized trial of higher goal hemoglobin after SAH         | Prospective, randomized pilot safety, and feasibility study                   | Packed RBC transfusion to goal Hgb 11.5 g/dL (N = 21)                           | Packed RBC transfusion to goal Hgb 10 g/dL (N = 23)                           | Primary outcomes: days of core temp > 100.4 F, ventillator-free days, hemoglobin level | Higher target Hgb resulted in more transfusions. No difference in safety endpoints. Number of MRI infarcts, NIHSS, and mRS similar between both groups at all timepoints                                           | Naidech et al., Neurocrit Care 2010 [46]                                    |
| The Albumin in Subarachnoid Hemorrhage multicenter pilot clinical trial:  | Open label, dose escalation study                                             | Albumin in 3 tier doses: 0.625 g/kg/d (N = 20), 1.25 g/kg/d (N = 20), 1.875 g/kg/d (N = 7) × 7 days (N = 47 total) | NA                                                                            | Primary outcomes: severe to life threatening heart failure, anaphylaxis         | Doses up to 1.25 g/kg/d × 7 days tolerated without dose-limiting complications. Trend toward better outcomes in 1.25 g/kg/d dose compared to 0.625 g/kg/d                                                  | Suarez et al., Stroke 2012 [47]                                            |
| Vasodilators—CRGP and endothelin receptor antagonist                       |                                                                               |                                                                                 |                                                                                |                                                                                 |                                                                                                                                                                                                       |                                                                           |
| Effect of calcitonin-gene-related peptide in patients with delayed       | Randomized, single-blind, controlled, multicenter study                       | Calcitonin-related gene peptide (0.6mcg/min) × 10 days (N = 62)                | Standard medical therapy (N = 55)                                              | Primary outcome: 3-month GOS                                                      | No difference in 3-month GOS. Hypotension common in treatment group.                                                                                                                                   | Bell, European CGRP in subarachnoid Hemorrhage study group, Lancet 1992   |
| surgical clipping: a randomized, double-blind, placebo-controlled phase 3 |                                                                               |                                                                                 |                                                                                |                                                                                 |                                                                                                                                                                                                       | [48]                                                                     |
| trial (CONSCIOUS 2)                                                      |                                                                               |                                                                                 |                                                                                |                                                                                 |                                                                                                                                                                                                       |                                                                           |
| Clazosentan, an endothelin receptor antagonist, in patients with          | Phase 3 randomized placebo-controlled double-blinded                          | Clazosentan (5 mg/h IV up to 14 days) (N = 748)                                | Placebo (N = 389)                                                              |                                                                                 | No effect on primary endpoint (21% in clazosentan group and 25% in placebo group P = NS). Poor outcome (GOS) in 29% clazosentan and 25% placebo group                                                                 | MacDonald et al., Lancet Neurol 2011 [49]                                  |
| aneurysmal SAH undergoing surgical clipping: a randomized, double-blind, |                                                                               |                                                                                 |                                                                                |                                                                                 |                                                                                                                                                                                                       |                                                                           |
| placebo-controlled phase 3 trial (CONSCIOUS 2)                           |                                                                               |                                                                                 |                                                                                |                                                                                 |                                                                                                                                                                                                       |                                                                           |
| Randomized trial of clazosentan in patients with aneurysmal subarachnoid | Phase 3 randomized placebo-controlled double-blinded; terminated early for   | Clazosentan (5 or 15 mg/h IV up to 14 days) (N = 194)                           | Placebo (N = 189)                                                             |                                                                                 | Clazosentan 15 mg/h significantly reduced vasospasm-related morbidity/all-cause mortality at 6 weeks but did not improve long-term outcome. Primary outcome: 24% in clazosentan 5 mg/h and 27% in placebo group P = NS and 15% in clazosentan 15 mg/h P = 0.007 Poor outcome in 25% of clazosentan 5 mg/h, 28% clazosentan 15 mg/h, and 24% of placebo group P = NS. | MacDonald et al., Stroke 2012 [50]                                        |
| hemorrhage undergoing endovascular coiling (CONSCIOUS 3)                 | (planned N = 1500)                                                            |                                                                                 |                                                                                |                                                                                 |                                                                                                                                                                                                       |                                                                           |
### Table 1: Continued.

| Trial name                                                                 | Study design                                                                 | Treatment group                                                                 | Control group                                                                 | Outcome measure                                                                 | Results                                                                                                                                                                                                 | Reference               |
|---------------------------------------------------------------------------|------------------------------------------------------------------------------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------|
| Effect of hypervolemic therapy on cerebral blood flow after subarachnoid hemorrhage: A randomized controlled trial | Randomized, controlled, single-center study                                  | High-volume management (with colloid and crystalloid) to target PADP ≥ 14 mmHg or CVP ≥ 8 mmHg \( (N = 41) \) | Normal volume management (with colloid and crystalloid) to target PADP ≥ 7 mmHg or CVP ≥ 5 mmHg \( (N = 41) \) | Primary outcome: CBF by Xenon CT and blood volume by tagged RBC Secondary outcomes: symptomatic vasospasm, medical complications, GOS and 3, 6, and 12 months | High-volume management patients received significantly more fluid but there was no effect on net fluid balance or blood volume. No difference in CBF or vasospasm | Lennihan et al., Stroke 2000 [51] |
| Prophylactic hyperdynamic postoperative fluid therapy after aneurysmal subarachnoid hemorrhage: a clinical, prospective, randomized, controlled trial | Randomized, controlled Prospective, trial of Hunt Hess I–III patients       | Hypertensive (MAP 20 mmHg greater than pre-op), hypervolemic (CVP 8–12 mmHg) and hemodilutional (Hct 30–35%) therapy \( (N = 16) \) | Normovolemic crystalloid fluid therapy until day 12 \( (N = 16) \) | Primary outcome: TCD vasospasm, CBF by SPECT on day 12 Secondary outcomes: 1 year GOS, neuropsych outcomes, and SPECT | No differences in TCD vasospasm or SPECT CBF. No difference in 1-year GOS, SPECT, or neuropsych outcomes | Egge et al., Neurosurgery 2001 [52] |

### Magnesium

| Intravenous magnesium sulfate for aneurysmal subarachnoid hemorrhage (IMASH): a randomized double-blinded, placebo-controlled, multicenter phase III trial | Randomized double-blinded, placebo-controlled, multicenter phase III trial | MgSO\(_4\) IV infusion to 2x baseline value \( (20 \text{ mmol} \times 30 \text{ minutes}) \) then continuous infusion of 80 mmol/d × 14 days; maximum allowed serum Mg of 2.5 mmol/L \( (N = 169) \) | Equivalent volume of normal saline infusion. Occasional changes in infusion rates to maintain blinding. \( (N = 158) \) | Primary outcome: 6-month GOSE 5–8 Secondary outcome: clinical vasospasm during initial 2 weeks, 6-month mRS, Barthel Index, and Short Form 36 | Favorable 6-month GOSE (5–8) 64% of Mg group and 63% placebo \( (P = NS) \) No difference in mRS, Barthel, Short Form 36, or clinical vasospasm. No subgroup differences | Wong et al., Stroke 2010 [53] |
| Magnesium for aneurysmal subarachnoid hemorrhage (MASH-2): a randomized placebo-controlled trial | Randomized, double-blind, placebo controlled, multicenter, phase III trial | MgSO\(_4\) IV 64 mmol/day \( (N = 606) \) | Placebo \( (N = 507) \) | Primary outcome: 3-month mRS 4–6 | No difference in poor outcome in the MgSO\(_4\) group (26.2% versus 25.3% in placebo group) | Mees et al., Lancet 2012 [54] |
| Trial name                                      | Study design                                      | Treatment group                         | Control group                         | Outcome measure                                                                 | Results                                                                                                               | Reference                        |
|-----------------------------------------------|--------------------------------------------------|-----------------------------------------|---------------------------------------|--------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------|----------------------------------|
| **Beneficial effects of adrenergic blockade in patients with subarachnoid hemorrhage** | Randomized controlled trial                      | Phentolamine 20 mg q 3 h + propranolol 80 mg q 8 × 3 weeks (N = 68) | Placebo (N = 66)                      | Primary outcome: neurological deficit at 28 days                                                                 | Trend toward less neurological deficit in the treated group (P = 0.053)                                              | Walter et al., BMJ 1982 [55] |
| **Endovascular therapy**                      |                                                   |                                         |                                       |                                                                                                                                       |                                                                                                                      | Zwiienenberg-Lee et al., Stroke 2008 [56] |
| Effect of prophylactic transluminal balloon angioplasty on cerebral vasospasm and outcome in patients with Fisher grade III subarachnoid hemorrhage: results of a phase II multicenter, randomized clinical trial | Unblinded, randomized phase II trial of Fisher III and Fisher III + IV SAH patients after clipping or coiling within 96 h of rupture | Balloon angioplasty of bilateral A1, M1, P1, basilar, intradural vertebral artery, and suprachondoid ICA. Protocol later revised to exclude A1 and P1 (N = 85) | No prophylactic balloon angioplasty (N = 85) | Primary outcome: 3-month GOS Secondary outcome: delayed ischemic neurological deficit, TCD vasospasm, ICU, and hospital length of stay | Nonsignificant difference in delayed ischemic neurological deficits but less therapeutic angioplasty required in treatment group (P = 0.03). No significant difference in GOS outcomes. LOS similar. Four patients had procedure related vessel perforation, three of whom died |                     |
| Rho kinase inhibitor—fasudil                   |                                                   |                                         |                                       |                                                                                                                                       |                                                                                                                      | Shibuya et al., J Neurosurg 1992 [57] |
| Effect of AT877 on cerebral vasospasm after aneurysmal subarachnoid hemorrhage. Results of a prospective placebo-controlled double-blind trial | Randomized, placebo controlled, double-blind, multicenter study in Hunt Hess I–IV clipped SAH patients | Fasudil (AT877) 30 mg IV over 30 minutes, TID × 14 days (N = 131) | Placebo (N = 136)                      | Primary outcome: reduction of incidence or severity of angiographic vasospasm, reduction of incidence and size of low-density CT lesions due to vasospasm, reduction of incidence of symptomatic vasospasm, poor outcome (1-month GOS) due to vasospasm | Fasudil significantly reduced angiographic vasospasm (38% in treatment group versus 61% in placebo group, P = 0.0023), infarcts reduced (16% in treatment versus 38% in placebo group, P = 0.0013) and symptomatic vasospasm reduced (35% in treatment versus 50% in placebo, P = 0.0247). Poor outcome (GOS 1–4) attributable to vasospasm occurred in 12% of treatment group and 26% of placebo group (P = 0.0152). No serious adverse events in fasudil group | Zhao et al., Neurol Med Chir (Tokyo) 2011 [58] |
| Efficacy and safety of fasudil in patients with subarachnoid hemorrhage: final results of a randomized trial of fasudil versus nimodipine | Randomized, open label, multicenter study of SAH Hunt-Hess grade I–IV clipped patients | Fasudil 30 mg IV TID × 14 days (N = 63) | Nimodipine 1-2 mg/h × 14 days (N = 66) | Primary outcome: symptomatic vasospasm or infarct on HCT Secondary outcome: 1-month GOS | No difference in symptomatic vasospasm or HCT infarcts. Improved GOS outcomes in fasudil group (good outcome in 74.5% versus 61.7% in nimodipine group, P = 0.040) |                     |
| Trial name                                                                 | Study design                                                                 | Treatment group                                                                                     | Control group                                                                                     | Outcome measure                                          | Results                                                                                                                                                                                                 | Reference |
|--------------------------------------------------------------------------|------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| The effect of intensive insulin therapy on infection rate, vasospasm,    | Randomized, controlled study                                                  | Intensive Insulin Infusion (80–120 mg/dL) × 14 d (N = 40)                                            | Conventional insulin infusion (glucose 80–220 mg/dL) × 14 d (N = 38)                               | Primary outcome: infection                                                                           | Higher infection rate in the conventional group (42% versus 27% in intensive group, \( P < 0.001 \)). Similar vasospasm, mortality, and mRS at 6 months | Bilotta et al., J Neurosurg Anesthesiol 2007 [59] |
| neurologic outcome and mortality in neurointensive care unit after        |                                                                               |                                                                                                     |                                                                                                   | Secondary outcomes: vasospasm, 6-month mortality, and mRS                                           |                                                                                                                                             |           |
| intracranial aneurysm clipping in patients with acute subarachnoid       |                                                                               |                                                                                                     |                                                                                                   |                                                                                                                                                |                                                                                                                                             |           |
| hemorrhage: a randomized prospective Pilot trial                         |                                                                               |                                                                                                     |                                                                                                   |                                                                                                                                                |                                                                                                                                             |           |
| Hypothermia                                                              |                                                                               |                                                                                                     |                                                                                                   |                                                                                                                                                |                                                                                                                                             |           |
| Mild intraoperative hypothermia during surgery for intracranial aneurysm  | Randomized, prospective, partially blinded, controlled, multicenter trial of | Intraoperative hypothermia (target 33°C with surface cooling) (N = 499)                              | Intraoperative normothermia (target 36.5°C) (N = 501)                                             | Primary outcome: GOS at 90 days                                                                      | No difference in 90 day GOS. Good GOS in 66% of hypothermia versus 63% of control patients (\( P = \text{NS} \)). No differences in death, length of stay, or discharge disposition. Postoperative bacteremia more common in the hypothermia group (5% versus 3%, \( P = 0.05 \)) | Todd et al., NEJM 2005 [60] |
| Trial name                                                                 | Study design                                           | Treatment group                      | Control group   | Outcome measure                                                                 | Results                                                                 | Reference                                      |
|---------------------------------------------------------------------------|--------------------------------------------------------|--------------------------------------|-----------------|---------------------------------------------------------------------------------|------------------------------------------------------------------------|-----------------------------------------------|
| Effects of nimodipine on cerebral blood flow and cerebrospinal fluid pressure after cardiac arrest: correlation with neurologic outcome | Randomized, double-blind study                         | Nimodipine IV 0.25 mcg/kg/min (N = 25) | Placebo (N = 26) | Primary outcome: CBF measured by Xenon CT Secondary outcomes: ICP, neurological disability | Higher CBF in nimodipine group in first 4 hours after arrest (P < 0.05) but no difference at 24 hours. No difference in neurological outcomes | Forsman et al., Anesth Analg 1989 [64] |
| Neuropsychological sequelae of cardiac arrest                              | Randomized, double-blind, placebo-controlled, study of out-of-hospital ventricular fibrillation | Nimodipine 10 mcg/kg IV then 0.5 mcg/kg/min × 24 hours (N = 35) | Placebo (N = 33) | Primary outcome: 3- and 12-month neuropsychological and cognitive batteries | No difference in neuropsychological or cognitive outcome between groups | Roine et al., JAMA 1992 [65] |
| A randomized clinical study of a calcium-entry blocker (lidoflazine) in the treatment of comatose survivors of cardiac arrest | Randomized, double-blind, placebo-controlled, multicenter study | Lidoflazine 1 mg/kg loading dose then 0.25 mg/kg at 8 and 16 hours after resuscitation (N = 259) | Placebo (N = 257) | Primary outcome: Pittsburgh Cerebral Performance Scale at 6 months Secondary outcomes: mortality, complications | No difference in 6-month neurological outcome or mortality between groups | Brain Resuscitation Clinical Trial II Study Group, NEJM 1991 [66] |
| Nimodipine after resuscitation from out-of-hospital ventricular fibrillation: a placebo-controlled, double-blind, randomized trial | Randomized, double-blind, placebo-controlled, study of out-of-hospital ventricular fibrillation | Nimodipine 10 mcg/kg IV then 0.5 mcg/kg/min × 24 hours (N = 75) | Placebo (N = 80) | Primary outcome: survival, 1-year GOS Secondary outcomes: death related to anoxic encephalopathy, GCS at 24 hours and 1 week, 3- and 12-month mini-mental state exam, activities of daily living, Barthel index, neurological exam, seizure, SPECT, myocardial infarction, arrhythmias | No difference in the survival rate, GOS at 3 or 12 months. No difference in minimental state exam, activities of daily living, or seizures | Roine et al., JAMA 1990 [67] |
| Coenzyme Q10 combined with mild hypothermia after cardiac arrest: a preliminary study | Randomized, placebo-controlled, double-blind, single-center study of out-of-hospital cardiac arrest | Hypothermia 35-36°C × 24 hours + Coenzyme Q 10 250 mg PO × 1 then 150 mg PO TID (N = 25) | Hypothermia 35-36°C × 24 hours + Placebo (N = 24) | Primary outcome: survival to ICU discharge Secondary outcomes: 3-month survival, 3-month GOS, S100 levels | 3-month survival was 68% in the treatment group and 29% in the control group (P = 0.0413). There was no significant difference in survival until discharge or GOS outcome | Damian et al., Circulation 2004 [68] |
| Trial name                                                                 | Study design                          | Treatment group                              | Control group     | Outcome measure                      | Results                                                                                                                                                                                                 | Reference                                      |
|---------------------------------------------------------------------------|---------------------------------------|----------------------------------------------|-------------------|--------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|
| A pilot randomized trial of thrombolysis in cardiac arrest (the TICA trial) | Randomized, double-blind, placebo controlled, single-center, feasibility trial for out-of-hospital cardiac arrest | Tenecteplase 50 mg IV × 1 (N = 19)            | Placebo (N = 16)  | Primary outcome: ROSC                | ROSC in 42% of tenecteplase and 6% of placebo group. No difference in survival to hospital discharge                                                                                                     | Fatovich et al., Resuscitation 2004 [69]     |
| Thrombolysis during resuscitation for out-of-hospital cardiac arrest      | Randomized, double-blind, controlled, multicenter study of out-of-hospital cardiac arrest | Tenecteplase 0.5 mg/kg IV (N = 525)           | Placebo (N = 525) | Primary outcome: survival at 30 days | No difference in 30-day survival, hospital admission, ROSC, 24-hour survival, discharge, or neurologic outcome. More intracranial hemorrhages in treatment group                                               | Böttiger et al., NEJM 2008 [70]              |
| Steroids and pressors                                                    |                                       |                                              |                   |                                      |                                                                                                                                                                                                     |                                               |
| Vasopressin, epinephrine, and corticosteroids for In-hospital cardiac arrest | Randomized, double-blind, placebo-controlled, single-center study | Vasopressin 20 IU IV + epinephrine 1 mg IV + methylprednisolone 40 mg IV followed by hydrocortisone (N = 48) | Epinephrine + placebo (N = 52) | Primary outcome: ROSC, survival to discharge | More ROSC in treatment group (81% versus 52%, \( P = 0.003 \)) and more survival to discharge (19% versus 4%, \( P = 0.02 \))                                                                 | Mentzelopoulos et al., Arch Intern Med 2009 [71] |
| Pressors                                                                 |                                       |                                              |                   |                                      |                                                                                                                                                                                                     |                                               |
| A comparison of standard-dose and high-dose epinephrine in cardiac arrest outside the hospital | Randomized, double-blind, prospective, multi-center study | Epinephrine 0.2 mg/kg IV (N = 648)            | Epinephrine 0.02 mg/kg IV (N = 632) | Primary outcome: return of spontaneous circulation (ROSC), admission to the hospital | No difference in ROSC rates, admission, survival, or discharge neurological status                                                                                                                       | Brown et al., NEJM 1992 [72]                 |
| Standard doses versus repeated high doses of epinephrine in cardiac arrest outside the hospital | Randomized, double-blind, prospective, single-center study | Repeated epinephrine 5 mg IV (N = 271)        | Repeated epinephrine 1 mg IV (N = 265) | Secondaries: admission to the hospital, discharge, cerebral performance category at discharge and 6 months | No difference in ROSC, admission, discharge, or 6-month neurological outcomes                                                                                                                         | Choux et al., Resuscitation 1995 [73]        |
| Trial name | Study design | Treatment group | Control group | Outcome measure | Results | Reference |
|------------|--------------|-----------------|---------------|----------------|---------|-----------|
| A randomised, double-blind comparison of methoxamine and epinephrine in human cardiopulmonary arrest | Randomized, double-blind, single-center study | Methoxamine 40 mg bolus IV then 40 mg 4 minutes later (N = 77) | Epinephrine 2 mg bolus then 2 mg IV q 4 min (N = 68) | Primary outcome: Mortality and Glasgow-Pittsburgh coma score Secondary outcomes: ROSC, successful resuscitation | No difference in ROSC or neurologic outcome, initial resuscitation, or survival to discharge | Patrick et al., Am J Respir Crit Care Med 1995 [74] |
| Randomised comparison of epinephrine and vasopressin in patients with out-of-hospital ventricular fibrillation | Randomized, double-blind, single-center, controlled study of out-of-hospital ventricular fibrillation patients who failed defibrillation | Vasopressin 40 IU IV (N = 20) | Epinephrine 1mg IV (N = 20) | Primary outcome: survival to admission Secondary outcome: 24-hour survival, survival to discharge, GCS at discharge | No significant difference in survival to admission but more vasopressin patients survived 24 hours (60% versus 20%, P = 0.02). No difference in survival to discharge or GCS at discharge | Lindner et al., Lancet 1997 [75] |
| High-dose versus standard-dose epinephrine treatment of cardiac arrest after failure of standard therapy | Randomized, controlled, single-blind, multicenter study of patients who had failed on standard dose of epinephrine 0.5–1.0 mg IV | Epinephrine 0.1 mg/kg IV up to 4 doses (N = 78) | Epinephrine 0.01 mg/kg IV up to 4 doses (N = 62) | Primary outcome: improvement in cardiac rhythm or ROSC Secondary outcomes: GCS at 6, 24, and 72 hours | No differences in ROSC, survival, or neurologic function between groups | Sherman et al., Pharmacotherapy 1997 [76] |
| A comparison of repeated high doses and repeated standard doses of epinephrine for cardiac arrest outside the hospital | Randomized, controlled, prospective multicenter study | Epinephrine 5 mg IV up to 15 doses at 3-minute intervals (N = 1677) | Epinephrine 1 mg IV up to 15 doses at 3-minute intervals (M = 1650) | Primary outcome: ROSC, admission to the hospital, number of admissions after a single dose of epinephrine, hospital discharge Secondary outcomes: survival, neurological outcome by GCS and cerebral performance scale | Significantly more ROSC in high dose group (40% versus 36% of control group, P = 0.02) and more survival to admission (26.5% versus 23.6% of controls, P = 0.05). No difference in survival to discharge or neurological status | Gueugniaud et al., NEJM 1998 [77] |
| Vasopressin versus epinephrine for in-hospital cardiac arrest; a randomized controlled trial | Randomized, controlled, triple-blind, multicenter study of in-hospital cardiac arrest for asystole, PEA, or refractory ventricular fibrillation | Vasopressin 40 IU IV (first pressor) (N = 104) | Epinephrine 1 mg IV (first pressor) (N = 96) | Primary outcome: survival for 1 hour Secondary outcomes: survival to hospital discharge, modified mini-mental state exam at discharge, cerebral performance score at discharge, ROSC, adverse events | No difference in survival at 1 hour or survival to hospital discharge. No difference in mini-mental state exam scores or cerebral performance scores | Stiell et al., Lancet 2001 [78] |
Table 2: Continued.

| Trial name | Study design | Treatment group | Control group | Outcome measure | Results | Reference |
|------------|--------------|-----------------|---------------|-----------------|---------|-----------|
| A comparison of vasopressin and epinephrine for out-of-hospital cardiopulmonary resuscitation | Randomized, controlled, multicenter study of out-of-hospital cardiac arrest with ventricular fibrillation failing defibrillation, PEA, or asystole | Vasopressin 40 IU IV × 2 doses maximum \((N = 589)\) | Epinephrine 1 mg IV × 2 doses maximum \((N = 597)\) | Primary outcome: survival to hospital admission | No difference in survival to admission among patients with ventricular fibrillation or PEA. Higher rates of hospital admission for asystole in vasopressin group \((29% \text{ versus } 20%, P = 0.02)\) and hospital discharge \((4.7% \text{ versus } 1.5% \text{ with epinephrine}, P = 0.04)\). Patients who received rescue epinephrine after vasopressin had better survival to admission and discharge than the epinephrine alone group. No difference in cerebral performance | Wenzel et al., NEJM 2004 [79] |
| Vasopressin and epinephrine versus epinephrine alone in cardiopulmonary resuscitation | Randomized, controlled, multicenter trial | Epinephrine 1 mg IV + Vasopressin 40 IU IV \((N = 1442)\) | Epinephrine 1 mg IV + Placebo \((N = 1452)\) | Primary outcome: Survival to hospital admission | No differences in survival to admission, ROSC, survival to discharge, 1-year survival, or good neurological recovery | Gueugniaud et al., NEJM 2008 [80] |
| Randomised trial of magnesium in in-hospital cardiac arrest (MAGIC trial) | Randomized, placebo-controlled, single-center study of cardiac arrest in the ICU or general ward | Magnesium 2 g IV bolus then 8 g over 24 hours \((N = 76)\) | Placebo \((N = 80)\) | Primary outcome: ROSC | No difference in ROSC, 24-hour survival, survival to discharge, or GCS | Thel et al., Lancet 1997 [81] |
| Trial name                                                                 | Study design                                                                 | Treatment group          | Control group          | Outcome measure                                                                 | Results                                                                 | Reference                      |
|--------------------------------------------------------------------------|-------------------------------------------------------------------------------|--------------------------|------------------------|---------------------------------------------------------------------------------|------------------------------------------------------------------------|--------------------------------|
| Magnesium in cardiac arrest (the MAGIC trial)                            | Randomized, double-blind, placebo-controlled, single-center study of out-of-hospital cardiac arrest | MgSO₄ 5g IV × 1 (N = 31) | Placebo (N = 36)       | Primary outcome: ECG rhythm 2 minutes after drug, ROSC                           | No differences in ROSC or survival                                   | Fatovich et al., Resuscitation 1997 [82] |
|                                                                          |                                                                               |                          |                        | Secondary outcomes: survival to ED, ICU, and hospital discharge                  |                                                                        |                                |
| Magnesium sulfate in the treatment of refractory ventricular fibrillation in the prehospital setting | Randomized, double-blind, placebo-controlled, multicenter study of prehospital ventricular fibrillation refractory to 3 shocks | MgSO₄ 2g IV × 1 (N = 58) | Placebo (N = 58)       | Primary outcome: ROSC                                                           | No difference in ROSC, survival to admission or discharge            | Allegra et al., Resuscitation 2001 [83] |
| A randomized trial to investigate the efficacy of magnesium sulphate for refractory ventricular fibrillation | Randomized, double-blind, placebo-controlled trial of ventricular fibrillation refractory to 3 shocks | MgSO₄ 2–4g IV × 1 (N = 52) | Placebo (N = 53)       | Primary outcome: ROSC                                                           | No differences in ROSC or survival to discharge                     | Hassan et al., Emerg Med J 2002 [84] |
|                                                                          | Tier 1: magnesium 2g IV + placebo (N = 75)                                   |                          |                        |                                                                                 |                                                                        |                                |
|                                                                          | Tier 2: diazepam 10mg IV + placebo (N = 75)                                  |                          |                        |                                                                                 |                                                                        |                                |
|                                                                          | Tier 3: magnesium 2g IV + Diazepam 10g IV (N = 75)                           |                          |                        |                                                                                 |                                                                        |                                |
|                                                                          | Primary outcome: awakening at 3 months (comprehensible speech and command following) Secondary outcome: days to awakening, days to death, independent at 3 months |                          |                        | No difference in neurological outcome between the 3 groups                      |                                                                        | Longstreth et al., Neurology 2002 [85] |
| Intravenous glucose after out-of-hospital cardiopulmonary arrest: a community-based randomized trial | Randomized, single-center controlled study                                   | 5% dextrose (D5W) infusion (N = 374) | 0.45 saline infusion (N = 374) | Primary outcome: command following or comprehensible speech                     | No difference in neurological outcomes, or survival to admission or discharge | Longstreth et al., Neurology 1993 [86] |
|                                                                          |                                                                               |                          |                        | Secondary outcomes: survival to hospital admission and discharge                 |                                                                        |                                |
| Trial name                                                                 | Study design                                                                 | Treatment group                                                                                           | Control group                                                                 | Outcome measure                                                                                                                                                                                                 | Results                                                                                       | Reference                                                                                     |
|---------------------------------------------------------------------------|------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|
| Strict versus moderate glucose control after resuscitation from ventricular fibrillation | Randomized, controlled, multicenter study of out-of-hospital ventricular fibrillation cardiac arrest | Strict glucose control (4–6 mmol/L) with insulin infusion × 48 hours (N = 39)                            | Moderate glucose control (6–8 mmol/L) with insulin infusion × 48 hours (N = 51) | Primary outcome: 30-day all-cause mortality after ROSC  Secondary outcomes: neuron-specific enolase levels at 24 and 48 hours | No difference in 30-day mortality                                                                | Oksanen et al., Intensive Care Med 2007 [87]                                                  |
| Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia | Randomized, controlled, single-blind, prospective study                     | Hypothermia 33°C × 12 h (N = 43)                                                                          | Normothermia 37°C (N = 34)                                                                                          | Primary outcome: discharge disposition  Secondary outcomes: adverse events, hemodynamic parameters                                                                 | Good discharge disposition in 49% of treatment group compared to 26% of normothermia group (P = 0.046). No difference in adverse events | Bernard et al., NEJM 2002 [88]                                                             |
| Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest | Randomized, controlled, single-blind, multicenter, prospective study        | Hypothermia 32–34°C × 24 h (N = 137)                                                                      | Normothermia 37°C (N = 138)                                                                                          | Primary outcome: 6 month neurologic outcome using Pittsburgh cerebral performance scale  Secondary outcome: 6-month mortality, complications at 7 days                                                                 | Hypothermia group had more favorable neurological outcome at 6 months (55% versus 39% of normothermia group, P = 0.009). Less death in hypothermia group (41% versus 55% in normothermia group, P = 0.02). No difference in complication rates | The hypothermia after cardiac arrest study group, NEJM 2002 [89]                             |
| Pilot randomized clinical trial of prehospital induction of mild hypothermia in out-of-hospital cardiac arrest patients with a rapid infusion of 4 degrees C normal saline | Randomized, controlled, safety and feasibility study of out-of-hospital cardiac arrest | 2 L 4°C normal saline infusion (N = 63)                                                                    | Standard care (N = 62)                                                                                                 | Primary outcome: esophageal temperature, adverse events  Secondary outcomes: awakening, hospital discharge                                                                 | Significant differences in temperature between groups (P < 0.001). No difference in awakening or hospital discharge | Kim et al., Circulation 2007 [90]                                                           |
| Prehospital therapeutic hypothermia for comatose survivors of cardiac arrest: a randomized controlled trial | Randomized controlled trial of out-of-hospital cardiac arrest               | 4°C Ringers solution 30 mL/kg to target temperature 33°C (N = 19)                                         | Conventional fluid therapy (N = 18)                                                                                   | Primary outcome: nasopharyngeal temperature  Secondary outcomes: hospital mortality and cerebral performance scale | Lower core temperature in the treatment group (P < 0.001). No difference in safety, mortality, or neurologic outcome | Kämärän et al., Acta Anaesthesiol Scand 2009 [91]                                           |
Table 2: Continued.

| Trial name                                                                 | Study design                                                                 | Treatment group                                                                 | Control group                                                                 | Outcome measure                                                                 | Results                                                                                                                                 | Reference                        |
|---------------------------------------------------------------------------|-------------------------------------------------------------------------------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|----------------------------------|
| Intra-arrest transnasal evaporative cooling: a randomized, prehospital, multicenter study (PRINCE: pre-rosc intranasal cooling effectiveness) | Randomized, controlled, prospective, single-blind, multicenter study for out-of-hospital arrest | Intra-arrest intranasal cooling with RhinoChill device + cooling at hospital arrival to 34°C \((N = 93)\) | Standard care with cooling at hospital arrival to 34°C \((N = 101)\)            | Primary Outcome: adverse events, length of stay, mechanical ventilation days, ROSC, survival to discharge, discharge Pittsburgh cerebral performance scale. | Time to target temperature was shorter in the intranasal cooling group \((P = 0.03)\). No difference in ROSC, survival of admitted patients, or neurologic outcome at discharge | Castrén et al., Circulation 2010 [92] |
| A comparison of active compression-decompression cardiopulmonary resuscitation with standard cardiopulmonary resuscitation for cardiac arrests occurring in the hospital | Randomized, controlled, single center study                                   | CPR using suction device (Ambu CardiPump) \((N = 29)\)                        | Standard CPR \((N = 33)\)                                                    | Primary Outcome: ROSC                                                      | ROSC occurred in 62% of treatment group versus 30% of control group \((P < 0.03)\) and 45% of treatment group survived 24 hours compared to 9% of control group \((P < 0.004)\). GCS at 24 hours was better in the treatment group \((P < 0.02)\) | Cohen et al., NEJM 1993 [93]      |
| The Ontario Trial of Active Compression-Decompression Cardiopulmonary Resuscitation for In-Hospital and Prehospital Cardiac Arrest | Randomized, single-blind, multicenter controlled trial of prehospital and in-hospital cardiac arrest | Active compression-decompression CPR using a suction device \((N = 906)\)       | Standard CPR \((N = 878)\)                                                  | Primary outcome: survival for 1 hour                                       | No differences in survival at 1 hour, survival until hospital discharge or mini-mental state exam for either prehospital or in-hospital arrest | Stiell et al., JAMA 1996 [94]      |
| Cardiopulmonary resuscitation by chest compression alone or with mouth-to-mouth ventilation | Randomized controlled study of out-of-hospital cardiac arrest                 | Bystander chest compression plus mouth to mouth resuscitation \((N = 279)\)    | Bystander chest compressions alone \((N = 241)\)                             | Primary outcome: survival to hospital discharge                              | Similar outcome with bystander chest compressions alone versus chest compressions with mouth to mouth | Hallstrom et al., NEJM 2000 [95]    |
| Constant flow insufflations of oxygen as the sole mode of ventilation during out-of-hospital cardiac arrest | Randomized, controlled study of out-of-hospital cardiac arrest               | Constant flow insufflations of oxygen \((N = 487)\)                         | Standard endotracheal intubation and mechanical ventilation \((N = 457)\)    | Primary outcome: survival to ICU discharge                                   | No difference in ROSC, hospital admission or ICU discharge. Higher \(O_2\) sat in continuous flow insufflation group | Bertrand et al., Intensive Care Med 2006 [96] |
| Compression-only CPR or standard CPR in out-of-hospital cardiac arrest    | Randomized, controlled, multicenter study of out-of-hospital cardiac arrest  | Compression only CPR \((N = 620)\)                                          | Standard CPR \((N = 656)\)                                                  | Primary outcome: 30 day survival                                             | Similar 30-day survival, 1-day survival and survival to hospital discharge                                                     | Svensson et al., NEJM 2010 [97]    |
| Trial name                                                                 | Study design                                                                 | Treatment group                                                                 | Control group                                                                 | Outcome measure                                                                                                                                  | Results                                                                                           | Reference                                                                                      |
|---------------------------------------------------------------------------|------------------------------------------------------------------------------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|
| CPR with chest compression alone or with rescue breathing                  | Randomized, controlled, multicenter study of out-of-hospital cardiac arrest  | Chest compressions alone (<em>N</em> = 981)                                    | -                                                                             | Primary outcome: survival to hospital discharge and Survival to discharge of cerebral performance score. Secondary outcome: ROSC.                | No difference in survival to hospital discharge or in neurologic outcome. Trend toward improved survival at discharge in those with cardiac cause of arrest and shockable rhythm (<em>P</em> = 0.09) | Rea et al., NEJM 2010 [98]                                                                     |
| Atrial of an impedance threshold device in out-of-hospital cardiac arrest  | Randomized, double-blinded, multicenter study of out-of-hospital cardiac arrest | Impedance threshold device (ITD) which increasing negative intrathoracic pressure and improves cardiac output (<em>N</em> = 4373) | Sham ITD (<em>N</em> = 4345)                                                  | Primary outcome: survival to hospital discharge with good mRS. Secondary outcome: survival to ED admission, hospital discharge, adverse events. | No difference in survival with good mRS.                                                      | Auferheide et al., NEJM 2011 [99]                                                               |
| Adenosine antagonist                                                       |                                                                               |                                                                               |                                                                               | Primary outcome: ROSC. Secondary outcomes: duration of ROSC, survival to admission, survival to discharge, length of stay, 24-hour tachyarrhythmias, 24-hour seizures, 1-year neurologic outcome by GCS, Glasgow-Pittsburgh cerebral and overall performance scales, modified mini-mental state exam, functional status questionnaire | No difference in ROSC. More tachyarrhythmias in the treatment group. Survival to hospital admission and survival to discharge were not different | Abu-Laban et al., Lancet 2006 [100]                                                              |
| Aminophylline in bradyasystolic cardiac arrest: a randomized placebo-controlled trial | Randomized, placebo-controlled, double-blind, multicenter study of asystole and PEA arrest unresponsive to epinephrine and atropine | Aminophylline 250 mg (<em>N</em> = 486)                                       | Placebo (<em>N</em> = 485)                                                      |                                                                               |                                                                                  |                                                                                               |
| Fluid management                                                           |                                                                               |                                                                               |                                                                               | Primary outcome: amount of fluid administered in 24 hours. Secondary outcome: MRI vasogenic edema                                                  | The treatment group required significantly less fluid than the control group. There was no difference in MRI brain edema | Heradstveit et al., Scand J Trauma Resusc Emerg Med 2010 [104]                                      |

**Table 2: Continued.**
| Trial name                                                                 | Study design                                                                 | Treatment group                  | Control group                  | Outcome measure                                                                 | Results                                                                                      | Reference                                                                                   |
|---------------------------------------------------------------------------|------------------------------------------------------------------------------|----------------------------------|-------------------------------|--------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------|
| Randomized clinical study of thiopental loading in comatose survivors of cardiac arrest | Randomized, controlled, multicenter study                                   | Thiopeptal 30 mg/kg IV load (N = 131) | Standard therapy (N = 131)    | Primary outcome: Pittsburgh cerebral Performance scale at 6 and 12 months Secondary outcomes: best neurological performance ever obtained during followup, time to recovery | No difference in neurological outcome or mortality between groups                               | Brain Resuscitation Clinical Trial I Study Group. NEJM 1986 [102]                             |
| Calcium                                                                   |                                                                               |                                   |                               |                                                                                |                                                                                               |                                                                                               |
| Calcium chloride: reassessment of use in asystole                          | Randomized, double-blind, placebo-controlled study in prehospital asystolic cardiac arrest refractory to epinephrine, bicarbonate, and atropine | Calcium chloride (N = 18)          | Placebo (N = 14)              | Primary outcome: ROSC Secondary outcome: hospital discharge                     | No difference in ROSC                                                                        | Stueven et al., Ann Emerg Med 1984 [103]                                                    |
| The effectiveness of calcium chloride in refractory electromechanical dissociation | Randomized, blinded, placebo-controlled study of prehospital PEA arrest refractory to epinephrine and bicarbonate | Calcium chloride (N = 48)          | Placebo (N = 42)              | Primary outcome: ROSC Secondary outcomes: survival to hospital discharge         | No difference in ROSC but subgroup of patients with widened QRS did have more ROSC in calcium group (P = 0.028) | Stueven et al., Ann Emerg Med 1985 [104]                                                    |
| Lack of effectiveness of calcium chloride in refractory asystole           | Randomized, blinded, placebo controlled study of prehospital asystolic cardiac arrest refractory to epinephrine, bicarbonate, and atropine | Calcium chloride (N = 39)          | Placebo (N = 34)              | Primary outcome: ROSC Secondary outcomes: survival to hospital discharge         | No difference in ROSC or hospital discharge                                                   | Stueven et al., Ann Emerg Med 1985 [105]                                                    |
| Sodium bicarbonate                                                        |                                                                               |                                   |                               |                                                                                |                                                                                               |                                                                                               |
| Buffer therapy during out-of-hospital cardiopulmonary resuscitation       | Randomized, double-blind, placebo-controlled study of out-of-hospital asystole or ventricular fibrillation refractory to first defibrillation attempt | Sodium bicarbonate 250 mL IV x 1 (N = 245) | Placebo (N = 257)           | Primary outcome: survival to ICU admission, survival to hospital discharge        | No difference in survival to ICU admission or hospital discharge                             | Dybvik et al, Resuscitation 1995 [106]                                                       |
| Trial name | Study design | Treatment group | Control group | Outcome measure | Results | Reference |
|------------|--------------|-----------------|---------------|----------------|---------|-----------|
| Sodium bicarbonate improves outcome in prolonged prehospital cardiac arrest | Randomized, double-blind, placebo-controlled trial of prehospital cardiac arrest | Sodium bicarbonate (1 meq/kg) IV x 1 (N = 175) | Placebo (N = 155) | Primary outcome: survival to ED | No difference in survival to ED admission or ROSC. Better survival with bicarbonate in the prolonged (>15 minute) arrest group (P = 0.007) | Vukmir and Katz, Am J Emerg Med 2006 [107] |
| Hemofiltration | Tier 1: hemofiltration (200 mL/kg/h) over 8 hours (N = 20) Tier 2: hemofiltration plus hypothermia to 32°C x 24 hours (N = 22) | Standard care (N = 19) | Primary outcome: survival at 6 months Secondary outcome: intractable shock, Pittsburgh cerebral performance scale | Significantly better survival compared to control in hemofiltration group (P = 0.026) and hemofiltration plus hypothermia group (P = 0.018). No difference in 6-month neurologic outcome | Laurent et al., J Am Coll Cardiol 2005 [108] |
| Rhythm analysis | Early rhythm analysis: 30–60 seconds of EMS CPR followed by ECG analysis (N = 5290) Later rhythm analysis: 180 seconds of EMS CPR followed by ECG analysis (N = 4643) | Primary outcome: survival to hospital discharge with mRS 0–3 Secondary outcomes: survival to discharge, survival to hospital admission, ROSC | No difference in outcome between a brief and longer period of CPR before ECG analysis of rhythm | | Stiell et al., NEJM 2011 [109] |
tested an intervention published in English between 1980 and 2012, were included. Only trials examining mortality or neurologic outcome as a primary or secondary endpoint were reviewed. Only trials specific to SAH (not trials that included other neurocritical diagnoses or brain injury diagnoses) were included. Cardiac arrest trials included both out-of-hospital and in-hospital arrest and all arrest rhythms were included. Post hoc analyses of existing trials were not reviewed. If phase III results of a trial were available, earlier phases of the same trial were not included in analysis unless the patient population or methodology differed substantially.

A PubMed search of the terms "subarachnoid hemorrhage" and "neurologic outcome" with the limits of human, age ≥ 18 years old, English and randomized, controlled trial yielded 23 results. A PubMed search of the term "subarachnoid hemorrhage" and "mortality" with the limits of human, age ≥ 18 years old, English and randomized, controlled trial yielded 78 results. An additional review of articles identified by a broader search of "subarachnoid hemorrhage" with the limits of human, age ≥ 18 years old, English and randomized, controlled trial yielded 244 results. Review of these studies yielded 57 aneurysmal SAH trials that met inclusion criteria and were analyzed. A Pubmed search of the terms "cardiac arrest" and "neurologic outcome" with the limits of human, English, age ≥ 18 years old, and randomized, controlled trial yielded 21 results. A PubMed search of the terms "cardiac arrest" and "mortality" with the limits of human, English, age ≥ 18 years old, and randomized, controlled trial yielded 197 results. Review of these studies yielded 46 cardiac arrest trials that met inclusion criteria and were analyzed.

Clinicaltrials.gov was searched for ongoing interventional trials in cardiac arrest and aneurysmal subarachnoid hemorrhage. Only ongoing studies that were open and recruiting or preparing to recruit were included. Terminated studies were excluded from review. A search of ongoing studies on clinicaltrials.gov for the term "subarachnoid hemorrhage", limited to interventional studies of adults ≥18 years old, produced 86 results and a search for the term "cardiac arrest" limited to interventional studies of adults with neurologic outcomes produced 46 results. Of these, 25 ongoing SAH trials and 14 cardiac arrest trials met the criteria for review.

3. Results

3.1. Trials Analyzed. A total of 142 trials (82 SAH, 60 cardiac arrest) met review criteria. Of these, 103 were published in peer-reviewed journals and 39 were ongoing studies. Fifty-seven published randomized, controlled studies were identified in the SAH population and 46 in the cardiac arrest population. These studies are reviewed in detail in Tables 1 and 2. Additionally, 25 ongoing SAH trials and 14 ongoing cardiac trials were reviewed (Tables 3 and 4).

3.2. Interventions Studied. The main hypothetical mechanisms of intervention tested in published SAH trials were related to treating or preventing delayed cerebral ischemia (N = 40, 70%), preventing aneurysm rebleeding (N = 5, 9%), improving aneurysm repair technique (N = 5, 9%), improving fluid balance (N = 2, 4%), and others (N = 3, 5%). Among ongoing SAH trials, mechanisms of study include treating or preventing delayed cerebral ischemia (N = 19, 76%), limiting rebleeding (N = 1, 4%), improving aneurysm repair (N = 1, 4%), seizure control (N = 2, 8%), and other (N = 2, 8%). There are no published or ongoing SAH clinical trials that focus on treating acute brain injury after aneurysm rupture.

Conversely, the main mechanisms of intervention studied in published cardiac arrest trials focused on acute intervention to treat and limit early brain injury. All 46 (100%) published cardiac arrest trials focused on the acute time frame (first few hours) after cardiac arrest. Interventions studied included decreasing cerebral metabolic demand with hypothermia or barbiturate (N = 12, 26%), high-quality chest compressions or pressor use to return cerebral blood flow (N = 16, 35%), electrolyte/metabolic optimization with calcium, magnesium, sodium bicarbonate or insulin administration (N = 12, 26%), neuroprotective drugs including calcium channel blockers (N = 5, 11%), thrombolysis to treat the underlying cause of cardiac arrest (N = 2, 4%) and other (N = 5, 11%). Among ongoing cardiac arrest trials, mechanisms of study include decreasing cerebral metabolic demand with hypothermia (N = 9, 64%), high-quality chest compressions to return cerebral blood flow (N = 2, 14%) electrolyte/metabolic optimization with magnesium (N = 1, 7%), neuroprotective drugs (N = 1, 7%), and monitoring cerebral oxygenation (N = 1, 7%). A detailed list of interventions from published and ongoing studies in both the SAH and cardiac arrest population are listed in Table 5.

3.3. Outcome Measures. The most common neurological outcomes assessed in the SAH trials were delayed cerebral ischemia (N = 24, 42%), functional outcome (Glasgow outcome scale, modified Rankin scale or functional outcome scale, N = 24, 42%), angiographic or transcranial Doppler vasospasm (N = 6, 11%), and death (N = 4, 7%). Among cardiac arrest trials, the most often assessed neurological outcomes were the Pittsburgh cerebral performance score (N = 18, 40%), Glasgow outcome score or modified Rankin Score (N = 4, 9%), Glasgow coma score (N = 4, 9%), awakening and command following (N = 3, 7%), cognitive or neuropsychological testing (N = 1, 2%), "disability" (N = 1, 2%), death (N = 13, 30%), discharge disposition (N = 1, 2%) and others (N = 1, 2%).

3.4. Trial Results. Of the clinical trials reviewed for SAH, 30% (17/57) showed that the intervention tested had a statistically significant impact on neurological outcome or mortality. These include studies of nimodipine [4–6, 8, 110], phase II data for nicardipine implants during aneurysm clipping [13], the neuroprotectants edavarone [21] and nizofenone [20], pravastatin [25], early aneurysm surgery [28], endovascular coiling [29–31], cilostazol [41], methylprednisolone [44], erythropoietin [45], and fasudil [57, 58]. Similarly, 30% (17/57) of studies showed a positive impact on delayed cerebral ischemia, infarction, angiographic or TCD vasospasm, though there was incomplete overlap with the
| Trial name | Study design | Treatment group | Control group | Target enrollment | Outcome measure | PI | Comments |
|------------|--------------|-----------------|---------------|-------------------|----------------|----|----------|
| Statins and cerebral blood flow in SAH | Randomized, double-blind efficacy study | Simvastatin 80 mg/d for 21 days | Placebo | 60 | Primary outcome: resting CBF and autoregulation 7–10 days after SAH | Michael Diringer, NCT00795288 | Uses PET to understand the mechanism of statin use in vasospasm |
| The role of statins in preventing cerebral vasospasm secondary to subarachnoid hemorrhage | Randomized, double-blind, parallel assignment | Simvastatin 80 mg PO qd × 21 days | Placebo | 80 | Primary outcome: 6-month clinical outcome | Eberval Figueiredo, NCT01346748 | — |
| Use of simvastatin for the prevention of vasospasm in aneurysmal subarachnoid hemorrhage | Randomized, double-blind, parallel assignment efficacy trial | Tier 1: Simvastatin 40 mg × 21 d or Tier 2: Simvastatin 80 mg × 21 d | Placebo | 150 | Primary outcome: 21-day GOS, mRS, and Barthel Index Secondary outcome: clinical vasospasm | Ben Roitberg, NCT00487461 | — |
| High-dose simvastatin for aneurysmal subarachnoid hemorrhage (HDS-SAH) | Randomized, parallel assignment, double-blind efficacy study | Simvastatin 80 mg PO × 21 days | Simvastatin 40 mg PO × 21 days | 240 | Primary outcome: delayed ischemic neurological deficit Secondary Outcomes: LFTs, rhabdomyolysis, 3-month mRS, cost effectiveness | George Wong, NCT01077206 | There may be a biochemical and neuroprotective dose-related relationship between simvastatin and delayed ischemic neurological deficits. |
| Simvastatin in aneurysmal subarachnoid hemorrhage (STASH): a multicentre randomised controlled clinical trial | Randomized, placebo-controlled, double-blind phase III trial | Simvastatin 40 mg PO qd × 21 days | Placebo | 1600 | Primary outcome: 6-month mRS Secondary outcome: need and intensity of delayed ischemic deficit rescue therapy, incidence and duration of delayed ischemic deficits, incidence and severity of sepsis, length of stay, discharge disposition | Peter Kirkpatrick, NCT00731627 | Simvastatin may improve CBF and inflammation following SAH |
| Trial name                                                                 | Study design                                                                 | Treatment group | Control group | Target enrollment | Outcome measure                                                                 | PI                                | Comments                                                                                                                                 |
|--------------------------------------------------------------------------|------------------------------------------------------------------------------|-----------------|---------------|------------------|--------------------------------------------------------------------------------|-----------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------|
| **Aneurysm repair**                                                      |                                                                              |                 |               |                  |                                                                                |                                   |                                                                                                                                         |
| International subarachnoid aneurysm trial II comparing clinical outcomes of Surgical clipping and endovascular coiling for ruptured intracranial aneurysms not included in the original ISAT study (ISAT II) | Randomized, open label, safety/efficacy study of WFNS I–IV                  | Surgical Clipping | Endovascular Coiling | 1724 | Primary outcome: 12-month mRS > 2 Secondary outcomes: ICH following treatment, failure of aneurysm occlusion, all cause morbidity and mortality, aneurysm recurrence, hospitalization > 20 days or discharge other than home, aneurysm rebleed | Tim Darsaut, Max Findlay, and Jean Raymond, NCT01668563 | ISAT included primarily small anterior circulation aneurysms. The optimal treatment of other locations and sizes of aneurysms remains unclear and coiling may not be as durable as clipping |
| **Lipid peroxidation inhibitor**                                         |                                                                              |                 |               |                  |                                                                                |                                   | Hemoglobin released from lysed RBCs oxidizes and generates protein radicals that induce lipid peroxidation. Metabolites of peroxidations (F2-isoprostanes) are potent vasoconstrictors. Acetaminophen can inhibit these metabolites and NAC can inhibit lipid peroxidation |
| Acetaminophen in aSAH to inhibit lipid peroxidation and cerebral vasospasm | Randomized, double-blind, placebo-controlled, safety/efficacy trial          | Group 1: Acetaminophen 1 g q 6 | Placebo 120 |                  | Primary outcome: F2-IsoP biomarkers for lipid peroxidation. Secondary outcome: vasospasm and brain ischemia as assessed by CTA/CTP or MRI DWI | John Oates, NCT00585559 |                                                                                                                                         |
|                                                                          |                                                                              | Group 2: Acetaminophen 1 g q6 + NAC 0.5 g/h |                        |                  |                                                                                |                                   |                                                                                                                                         |
|                                                                          |                                                                              | Group 3: Acetaminophen 1.5 g q6 + NAC 0.5 g/h |                        |                  |                                                                                |                                   |                                                                                                                                         |
|                                                                          |                                                                              | Group 4: Acetaminophen 1 g q6 + NAC 0.5 g/h |                        |                  |                                                                                |                                   |                                                                                                                                         |
| **Neuroprotective drugs**                                                |                                                                              | Tiopronin       | Placebo 60    |                  | Primary outcome: serum and CSF 3AP levels Secondary outcomes: 12 month mRS, Barthel, Lawton, NIHSS, TICS adverse events Primary outcome: TCD vasospasm, duration of impaired autoregulation measured by TCD Secondary Outcomes: LDL, oxy-LDL, CRP, circulating endothelial cells, endothelial progenitor cells | E Sander Connolly, NCT01095731 | 3AP is toxic metabolite produced during cerebral ischemia. It is neutralized by tiopronin                                                                 |
| Effects of tiopronin on 3-aminopropanal level and neurologic outcome after aneurysmal SAH | Randomized, double-blind, phase 2 bioavailability                          | Tiopronin       | Placebo 60    |                  |                                                                                |                                   |                                                                                                                                         |
| Lycopene following aneurysmal subarachnoid haemorrhage (LASH)           | Randomized, double-blind, placebo-controlled, efficacy study               | Lycopene 30 mg PO qd x 21 days | Placebo 124  |                  |                                                                                | Karol Budohoski, NCT00905931 | Lycopene is a natural antioxidant that may reduce vascular injury and inflammation and limit vasospasm                                                                 |
### Table 3: Continued.

| Trial name                                                                 | Study design                                                                 | Treatment group               | Control group             | Target enrollment | Outcome measure                                                                 | PI                                      | Comments                                                                 |
|----------------------------------------------------------------------------|------------------------------------------------------------------------------|-------------------------------|--------------------------|-------------------|--------------------------------------------------------------------------------|-----------------------------------------|--------------------------------------------------------------------------------|
| **Thrombolitics**                                                          |                                                                              |                               |                          |                   |                                                                                |                                         |                                                                         |
| Intraventricular tPA in the management of aneurysmal subarachnoid hemorrhage | Randomized, placebo-controlled, double-blind safety trial                   | tPA intraventricular q 12 h × 5 doses | Placebo administered q 12 h × 5 doses | 12                | Primary outcome: HCT rate and variance of ventricular and cisternal clot clearance  
Secondary outcome: hemorrhagic complications, ventriculo(stomy)-related infections, TCD vasospasm, CT angio vasospasm, symptomatic vasospasm, CSF cytokines and coagulation measurements, ICP, fever burden, volume of CSF drainage, 6-month GOSE and EuroQOL | Andreas Kramer, NCT01098890 | Intraventricular TPA may accelerate clearance of IVH ameliorating vasospasm, hydrocephalus, and ICP |
| Effect of red blood cell transfusion on brain metabolism in patients with SAH | Open label safety/efficacy study in SAH patients with Hgb < 12.5 g/dL and DCI, high risk for vasospasm or angiographic vasospasm | Transfusion of 1 unit of packed RBC over 1 hour | NA                       | 48                | Primary outcome: percent of brain regions with low oxygen delivery before and 1 hour after transfusion  
Secondary outcomes: relationship of oxygen delivery and angiographic vasospasm | Michael Diringer, NCT00968227 | Uses PET to assess the relationship between Hct and oxygen delivery in SAH patients |
| Sildenafil for prevention of cerebral vasospasm (SIPCEVA)                   | Randomized, placebo-controlled, safety and efficacy study                    | Tier 1: sildenafil 25 mg PO TID day 3–14 after SAH  
Tier 2: sildenafil 50 mg PO TID day 3–14 after SAH | Placebo                       | 18                | Primary outcome: New neurological deficit due to vasospasm up to 14 days after SAH  
Secondary outcomes: TCD spasm, mortality, adverse drug effects, length of stay, discharge mRS  
Primary outcome: tolerability, hyponatremia  
Secondary outcomes: liver toxicity, hemodynamics, ICP, TCD, angiographic vasospasm treatments, 90-day GOS, mRS, and Barthel | Andre Cerutti Franciscatto, NCT0099870 | —                                                                        |
| Safety study of dantrolene in SAH                                          | Randomized, double-blind safety study                                         | Dantrolene                     | Placebo                   | 30                | Dantrolene is a muscle relaxant that may ameliorate vascular muscle tone and limit vasospasm | Susanne Muehlshlegel, NCT0102-0972 | —                                                                        |
| Trial name                                              | Study design                                                                 | Treatment group                                                                 | Control group         | Target enrollment | Outcome measure                                                                 | PI                                      | Comments                                                                 |
|--------------------------------------------------------|------------------------------------------------------------------------------|---------------------------------------------------------------------------------|-----------------------|-------------------|---------------------------------------------------------------------------------|-----------------------------------------|--------------------------------------------------------------------------------|
| Safety and pharmacokinetic evaluation of nitrite for prevention of cerebral vasospasm | Randomized, single-blind, parallel assignment safety study                    | Tier 1: sodium nitrite 32 nmol/kg/min Tier 2: sodium nitrite 48 nmol/kg/min Tier 3: sodium nitrite 64 nmol/kg/min | Placebo vehicle 18   |                   | Primary outcome: pharmacokinetics of 14-day sodium nitrite infusion Secondary outcomes: safety and efficacy | Edward Oldfield, NCT00873015            | —                                                                                 |
| Effects of prostacyclin infusion on cerebral vessels and metabolism in patients with subarachnoid hemorrhage | Randomized, placebo controlled, double-blind, parallel assignment, pharmacodynamics study | Tier 1: prostacyclin 1 ng/kg/min day 5–10 after SAH Tier 2: prostacyclin 2 ng/kg/min day 5–10 after SAH | Placebo, IV infusion day 5–10 after SAH 90 |                   | Primary outcome: vasospasm measured by CT perfusion Secondary outcomes: cerebral metabolism measured by microdialysis, 3-month GOS, clinical vasospasm, brain tissue oxygen, CT angio vasospasm, MAP, serum S100b | Rune Rasmussen, NCT01447095 | Prostacyclin may cause vasodilation and ameliorate vasospasm |
| Hypertensive, hypervolemic therapy                      |                                                                              |                                                                                  |                       |                   |                                                                                 |                          |                                                                                  |
| Induced hypertension for treatment of delayed cerebral ischemia after aneurysmal SAH HIMALAIA | Randomized, Single blind safety/efficacy study of patients with SAH and DCI (clinically defined) | Induced hypertension with vasopressors and fluids for 48 hours No induced hypertension 240 |                       |                   | Primary outcome: mRS at 3 months Secondary outcomes: proportion of treated patients who did not have clinical improvement of DCI symptoms within 24 hours, 30-day mortality, 3-month Barthel, SSQoL, hospital anxiety and depression scale, cognitive failures questionnaire, hospital complications, CTP results, medical costs | Arjen Slooter and Walter van den Bergh, NCT016B235 | CBF measured in all patients using CTP at enrollment and 24–36 hours |
| Intensive management of pressure and volume expansion in patients with subarachnoid hemorrhage (IMPROVES) | Randomized, single-blind, factorial assignment                               | Tier 1: hypervolemia + conventional blood pressure Tier 2: normovolemia + hypertension Tier 3: hypervolemia + hypertension | Normal volume, normal blood pressure 20 |                   | Primary outcome: achievement of hemodynamic goals in each group | Miriam Treggiari, NCT0414894 | Though triple H is a common therapy, its safety and efficacy have not been well quantified |
| Trial name                                                                 | Study design                        | Treatment group                                           | Control group                      | Target enrollment | Outcome measure                                                                 | PI                                      | Comments                                                                 |
|---------------------------------------------------------------------------|-------------------------------------|-----------------------------------------------------------|-----------------------------------|------------------|---------------------------------------------------------------------------------|----------------------------------------|--------------------------------------------------------------------------|
| EARLYDRAIN: outcome after early lumbar CSF: drainage in aneurysmal subarachnoid hemorrhage | Randomized, 2-arm controlled trial | Continuous lumbar CSF drainage of 120 mg qd × 7 d         | Standard NICU care                | 300               | Primary outcome: 6-month mRS                                                                 | Bardutzky J, NCT01258257              | Lumbar drainage to remove blood from the basal cisterns may limit delayed cerebral ischemia |
| Cerebrospinal fluid (CSF) drainage study                                  | Randomized, open label, parallel assignment study of SAH patients requiring external ventricular drainage (EVD) | High volume CSF diversion (EVD at 5 mmHg) × 10 days        | Conventional CSF diversion (EVD at 15 mmHg), weaned at physician discretion | 20               | Secondary Outcome: radiologic infarction, TCD or angiographic vasospasm, shunt placement, ventriculitis, discharge mRS, 90 day mini-mental status exam, length of stay | Giuseppe Lanzino, NCT01420978         | More aggressive CSF drainage may improve brain microcirculation and perfusion and lead to better neurological outcomes |
| Comparison of short duration levetiracetam to extended course for seizure prophylaxis after subarachnoid hemorrhage | Randomized, prospective, open label, parallel assignment, phase III, safety/efficacy study | Levetiracetam 1000 mg BID × 3 days                        | Levetiracetam 1000 mg BID × hospital stay | 460               | Primary outcome: In hospital seizures Secondary outcome: Incidence of seizure after hospital discharge, adverse drug reactions, length of stay, cognitive and functional outcomes | Rajat Dhar, NCT01137110               | Antiepileptics can have long-term cognitive side effects. A short course may be just as efficacious as prolonged use |
| Antiepileptic drugs and vascular risk markers                            | Randomized, open label, parallel assignment study | Tier 1: phenytoin 5 mg/kg/d divided in 2 doses Tier 2: valproate 15 mg/kg/d divided in 3 doses Tier 3: levetiracetam 1000-1500 mg/d divided in 2 doses | No drug intervention              | 200               | Primary outcome: serum cholesterol, non-HDL cholesterol, HDL, lipoprotein a, CRP Secondary outcome: acute seizures, late seizures, mRS at 8 and 16 weeks | Prema Kishna and Scott Mintzer, NCT00774306 | Certain seizure medications may raise cholesterol levels and increase the risk of heart attack and stroke |
| Trial name                                                                 | Study design                                                                 | Treatment group          | Control group          | Target enrollment | Outcome measure                                                                 | PI                                      | Comments                                                                 |
|---------------------------------------------------------------------------|------------------------------------------------------------------------------|--------------------------|------------------------|--------------------|--------------------------------------------------------------------------------|-----------------------------------------|--------------------------------------------------------------------------------|
| Effects of dexmedetomidine on inflammatory cytokines in patients          | Randomized, open label, parallel assignment efficacy study                    | Dexmedetomidine 0.2–1.5 mcg/kg/h | Propofol 5–80 mcg/kg/min | 10                 | Primary outcome: serum and CSF cytokines over 48 hours                          | Shaun Keegan and Brittany Woolf, NCT01565590 | Dexmedetomidine may cause less inflammation over time than propofol          |
| methods in patients with aneurysmal subarachnoid hemorrhage               |                                                                              |                          |                        |                    | Secondary outcomes: sedative and analgesic requirements, RASS and CAM-ICU scores, length of stay, delayed cerebral ischemia, GOSE at discharge |                          |                                                                              |
| Rehabilitation                                                             | Nonrandomized, open label, parallel assignment                               | Early multidisciplinary rehab and mobilization | No intervention | 160                 | Primary outcome: 10-week GOS                                                     | Tanja Karic and Angelika Sorteberg, NCT01656317 | Early rehab may reduce complications and improve physical and cognitive function after SAH |
| Blood pressure control                                                    | Open label, safety, efficacy study, single group assignment (Phase 2)         | Clevidipine IV 2–32 mg/h for 24–48 hours | NA                     | 20                  | Primary: Blood pressure within target range                                     | Panayiotis Varelas, NCT00978822 | To assess how rapidly and safely Clevidipine can be used to control blood pressure in SAH patients. |
| Other                                                                     | Nonrandomized, open label                                                   | Spinal cord stimulation using MTS Trial System 3510 | NA                     | 12                  | Primary outcome: cerebral vasospasm                                             | Konstantin Slavin, NCT00766844       |                                                                              |
### Table 4: Randomized controlled trials assessing neurologic outcomes after cardiac arrest—ongoing trials.

| Trial name                                                                 | Study design                                                                 | Treatment group                          | Control group | Target enrollment | Outcome measure                                                                 | PI                                           | Comments                                                                                   |
|---------------------------------------------------------------------------|------------------------------------------------------------------------------|------------------------------------------|---------------|------------------|--------------------------------------------------------------------------------|---------------------------------------------|--------------------------------------------------------------------------------------------|
| **Neuroprotective drugs**                                                 |                                                                              |                                          |               |                  | Primary outcome: neuron-specific enolase                                        | Vanessa Stadlbauer and Karlheinz Smolle, NCT01390506 | Selenium can reduce oxidative stress after cardiac arrest and reduce inflammation          |
| Selenium to Improve Neurological Outcome after Cardiac Arrest (SCPR)      | Randomized, double-blind, placebo-controlled, single-center, phase 2a efficacy study | Sodium-selenite infusion × 7 days        | Placebo       | 52               | Secondary outcomes: inflammation and oxidative stress markers, NIHSS and Glasgow Pittsburgh performance score at 6 months, selenium blood levels, glutathione peroxidase plasma levels |                                                      |                                                                                            |
| Clinical Study of the LRS ThermoSuit System in Post Arrest Patients with Intravenous Infusion of Magnesium Sulfate | Randomized, double-blind, parallel assignment, safety/efficacy study of any rhythm | ThermoSuit to target 34°C plus magnesium sulfate IV (30 mg/kg over 15 minutes) | ThermoSuit to target 34°C plus placebo (normal saline) | 14               | Primary outcome: cooling rate                                                    | Michael Holzer and Andreas Janata, NCT00593164 | Tests new device to achieve therapeutic hypothermia and the impact of magnesium on cooling performance and hemodynamics |
| **Hypothermia**                                                           |                                                                              |                                          |               |                  | Secondary outcomes: time to target temperature, percentage of time in target temperature range, shivering, length of stay, neurologic status at discharge and 6 months, adverse events, survival at 24 hours, discharge and 30 days |                                                      |                                                                                            |
| Target Temperature Management after Cardiac Arrest (TTM)                  | Randomized, double-blind, parallel assignment, multicenter, safety/efficacy trial for out-of-hospital cardiac arrest | Target temperature 36°C × 24 h           | Target temperature 33°C × 24 h | 850              | Primary outcome: All cause mortality                                              | Niklas Nielsen and Hans, Friberg NCT01020916 | Attempts to identify optimal hypothermia target temperature                                |
Table 4: Continued.

| Trial name                                                                 | Study design                                                                 | Treatment group                                                                 | Control group                                                                 | Target enrollment | Outcome measure                                                                 | PI                                                                 | Comments                                                                 |
|---------------------------------------------------------------------------|------------------------------------------------------------------------------|---------------------------------------------------------------------------------|-------------------------------------------------------------------------------|-------------------|---------------------------------------------------------------------------------|----------------------------------------------------------------------|--------------------------------------------------------------------------|
| Hypothermia After in-Hospital Cardiac Arrest (HACA in hospital)            | Randomized, single-blind, parallel assignment, single-center, safety/efficacy study for in-hospital arrests of any rhythm | Mild therapeutic hypothermia 32–34°C × 24 hours.                                | Standard care, no hypothermia                                                 | 440               | Primary outcome: all cause mortality at 6 months                                  | Sebastian Wolfrum and Volkhard Kurowski, NCT00457431                  | Tests whether hypothermia treatment will improve outcome after in-hospital arrest of any rhythm |
| Intra-arrest Therapeutic Hypothermia in Prehospital Cardiac Arrest (HITUPPAC-BIO) | Randomized, open label, parallel assignment, efficacy trial                  | Hypothermia induction prehospital                                              | Hypothermia induction at hospital arrival                                    | 250               | Primary outcomes: brain injury biomarkers at 72 h                                | Guillaume Debaty Jean Francois Timsit, NCT00886184                     | Assess utility of early hypothermia prehospital                           |
| Induction of Mild Hypothermia Following Out-of-hospital Cardiac Arrest     | Randomized, open label, single group assignment, efficacy study of any rhythm out of hospital arrest | Rapid infusion of 2 L of 4°C normal saline prior to ED arrival                 | Standard therapy                                                             | 1364              | Primary outcome: awake and command following at hospital discharge               | Francis Kim, NCT0039469                                               | Tests whether rapid induction of hypothermia with cold saline infusion is efficacious |
| Comparing Therapeutic Hypothermia Using External and Internal Cooling for Post-Cardiac Arrest Patients | Randomized, open label, parallel assignment, efficacy trial | External device (Arctic Sun) induced hypothermia                              | Internal device (Alsius) induced hypothermia                                | 51                | Primary outcome: Survival to hospital discharge                                   | Marcus Ong, NCT00827957                                               | Identifying the most efficient method of cooling may improve outcome after cardiac arrest |
| Hypothermia + ECMO                                                        |                                                                              |                                                                                |                                                                                |                   | Primary outcome: survival to hospital discharge                                  | Stephen Bernard and Dion Stub, NCT01186614                              | Aggressive resuscitation may improve outcome in patients who fail standard resuscitation |
| Refractory Out-of-Hospital Cardiac Arrest Treated with Mechanical CPR, Hypothermia, ECMO and Early Reperfusion (CHEER) | Nonrandomized, single group, open label, safety/efficacy trial for patients who fail standard resuscitation | Automated CPR, ECMO, coronary angiography, therapeutic hypothermia             | NA                                                             | 24                | Primary outcomes: cerebral performance Scale, time to ECMO insertion, neurologic biomarkers, cardiac recovery | Stephen Bernard and Dion Stub, NCT01186614                              | Aggressive resuscitation may improve outcome in patients who fail standard resuscitation |
| Trial name                                                                 | Study design                                                                 | Treatment group                                                                 | Control group                  | Target enrollment | Outcome measure                                                                 | PI                                             | Comments                                      |
|---------------------------------------------------------------------------|------------------------------------------------------------------------------|--------------------------------------------------------------------------------|--------------------------------|-------------------|--------------------------------------------------------------------------------|------------------------------------------------|------------------------------------------------|
| Hyperinvasive approach to out-of-hospital cardiac arrest using mechanical chest compression device, prehospital intraarrest cooling, extracorporeal Life support and early Invasive assessment compared to standard of care: Prague OHCA Study | Randomized, open-label, parallel group, safety/efficacy study                | Prehospital mechanical compression device, intraarrest cooling and in hospital ECLS (compression device, Rhinochill, PLS ECMO) | Standard care       | 170                | Primary outcome: composite endpoint of survival with good neurological outcome (cerebral performance scale) Secondary outcome: 30 day cerebral performance scale, 30 day cardiac recovery | Jan Belohlavek and Ondrej Smid, NCT01511666  | Aggressive, early intervention may improve cerebral outcomes |
| Emergency Preservation and Resuscitation (EPR) for Cardiac Arrest from Trauma (EPR-CAT) | Nonrandomized, open label, parallel assignment, safety/efficacy study         | Profound hypothermia $<10^\circ C$ with cold saline infusion into aorta followed by resuscitation/rewarming with cardiopulmonary bypass | Standard treatment | 20                 | Primary outcome: survival to hospital discharge without major disability by GOSE Secondary outcomes: achieving target temperature in 1 hour, 28 day survival, 6 month neurological function, multiple organ system dysfunction | Samuel Tisherman, NCT01042015                 | Resuscitation technique for trauma patients that have arrested from exsanguination |

**Hypothermia + xenon**

| Trial name                                                                 | Study design                                                                 | Treatment group                                                                 | Control group                  | Target enrollment | Outcome measure                                                                 | PI                                             | Comments                                      |
|---------------------------------------------------------------------------|------------------------------------------------------------------------------|--------------------------------------------------------------------------------|--------------------------------|-------------------|--------------------------------------------------------------------------------|------------------------------------------------|------------------------------------------------|
| Effect of xenon and therapeutic hypothermia on brain and on neurological outcome following brain ischemia in cardiac arrest patients nonperfusing ventricular tachycardia (Xe-hypotheca) | Randomized, open label, parallel assignment, phase 2 safety/efficacy trial for ventricular fibrillation and nonperfusing ventricular tachycardia | Hypothermia $33^\circ C \times 24$h and Xenon inhalation $\times 24$h target end tidal $40\%$ | Hypothermia $33^\circ C \times 24$h | 110                | Primary outcome: PET and MRI ischemia at 24 hours and 10 days Secondary outcomes: neurological outcome at 6 months, TTE | Timo Laitio, NCT00879892                          | Xenon may be synergistically neuroprotective in combination with hypothermia post arrest by limiting cerebral hypoxia, neuronal loss, and mitochondrial dysfunction |

**Chest compressions**

| Trial name                                                                 | Study design                                                                 | Treatment group                                                                 | Control group                  | Target enrollment | Outcome measure                                                                 | PI                                             | Comments                                      |
|---------------------------------------------------------------------------|------------------------------------------------------------------------------|--------------------------------------------------------------------------------|--------------------------------|-------------------|--------------------------------------------------------------------------------|------------------------------------------------|------------------------------------------------|
| Continuous chest compressions                                              | Randomized, open label, multicenter, crossover assignment study of out-of-hospital cardiac arrest of any rhythm | Continuous chest compressions with ventilation 30:2                            | Continuous chest compressions  | 23600              | Primary outcome: survival to hospital discharge Secondary outcomes: mRS at discharge, adverse events | Myron Weisfeldt, NCT01372748                  | Continuous CPR without interruption for ventilation may be superior to interrupted compression with ventilation ratio of 30 : 2 |
| Trial name                                                                 | Study design                             | Treatment group                                                                 | Control group                                                                 | Target enrollment | Outcome measure                                                                                                                                                                                                 |
|---------------------------------------------------------------------------|------------------------------------------|---------------------------------------------------------------------------------|--------------------------------------------------------------------------------|-------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| LUCAS chest compressor versus manual chest compression in out-of-hospital | Randomized, open label, parallel assignment, efficacy study | Mechanical continuous chest compressions performed by LUCAS device               | Manual chest compressions                                                    | 400               | PI: Francesc Carmona Jimenez, Rosa-Maria Lidon, NCT01521208
Mechanical chest compression may be superior to manual chest compression. Primary outcome: survival to hospital admission, survival to discharge with good neurological state by cerebral performance scale. Secondary outcomes: ROSC, end tidal CO₂, SOFA scale, length of stay, metabolic and inflammatory markers, LV function. |
| cardiac arrest: LUCAT trial                                               |                                          |                                                                                 |                                                                              |                   |                                                                                                                                                                                                             |
| Cerebral Oxygenation in Cardiac Arrest and Hypothermia                    | Open label, safety and efficacy study    | Near-infrared monitoring                                                        | Standard therapy, no monitoring                                              | 70                | PI: Christian Storm, NCT0153426 Near-infrared spectroscopy (NIRS) could be a new-noninvasive marker for outcome after cardiac arrest. Low NIRS may correlate with poor outcome. |

**Cerebral oxygenation**

**Table 4: Continued.**
Table 5: Number of randomized, controlled trials published and ongoing for aneurysmal subarachnoid hemorrhage and cardiac arrest.

| Intervention                                         | Published N (%) | Ongoing N (%) | Published N (%) | Ongoing N (%) |
|------------------------------------------------------|-----------------|---------------|-----------------|---------------|
| Calcium channel blockers                             | 10 (18)         | 0             | 4 (9)           | 0             |
| Antifibrinolytics                                    | 5 (9)           | 0             | 0               | 0             |
| Neuroprotective drugs                                | 5 (9)           | 2 (8)         | 1 (2)           | 1 (7)         |
| Statins                                              | 4 (7)           | 5 (20)        | 0               | 0             |
| Aneurysm clip or coil                               | 4 (7)           | 1 (4)         | NA              | NA            |
| Lipid peroxidation inhibitor                         | 4 (7)           | 1 (4)         | 0               | 0             |
| Thrombolytics                                        | 3 (5)           | 1 (4)         | 2 (4)           | 0             |
| Antiplatelets                                        | 3 (5)           | 0             | 0               | 0             |
| Steroids                                             | 3 (5)           | 0             | 1 (2)           | 0             |
| Transfusion/blood products/erythropoietin            | 3 (5)           | 1 (4)         | 0               | 0             |
| Vasodilators                                         | 3 (5)           | 4 (16)        | 0               | 0             |
| Pressors or HHH                                      | 2 (4)           | 2 (8)         | 9 (19.5)        | 0             |
| Magnesium                                            | 2 (4)           | 0             | 5 (11)          | 1 (7)         |
| Rho-kinase inhibitor (fasudil)                       | 2 (4)           | 0             | 0               | 0             |
| Adrenergic blockade                                  | 1 (2)           | 0             | 0               | 0             |
| Endovascular therapy                                 | 1 (2)           | 0             | NA              | NA            |
| Insulin/glucose control                              | 1 (2)           | 0             | 2 (4)           | 0             |
| Hypothermia                                          | 1 (2)           | 0             | 5 (11)          | 9 (64)        |
| CSF diversion                                        | 0               | 2 (8)         | 0               | 0             |
| Antiepileptics                                       | 0               | 2 (8)         | 0               | 0             |
| Sedation                                             | 0               | 1 (4)         | 0               | 0             |
| Rehabilitation                                       | 0               | 1 (4)         | 0               | 0             |
| Blood pressure                                       | 0               | 1 (4)         | 0               | 0             |
| Other                                                | 0               | 1 (4)         | 0               | 0             |
| Chest compressions                                   | NA              | NA            | 7 (15)          | 2 (14)        |
| Adenosine antagonist                                 | 0               | 0             | 1 (2)           | 0             |
| Fluid management                                     | 0               | 0             | 1 (2)           | 0             |
| Barbiturate                                          | 0               | 0             | 1 (2)           | 0             |
| Cerebral oxygenation                                 | 0               | 0             | 0               | 1 (7)         |
| Calcium chloride                                     | 0               | 0             | 3 (7)           | 0             |
| Sodium bicarbonate                                   | 0               | 0             | 2 (4)           | 0             |
| Hemofiltration                                       | 0               | 0             | 1 (2)           | 0             |
| Rhythm analysis                                      | 0               | 0             | 1 (2)           | 0             |
| Total                                                | 57              | 25            | 46              | 14            |
hypothermia for ventricular fibrillation and pulseless ventricular tachycardia arrests [88, 89], and one study of active compression-decompression CPR [93], though a larger study of active compression-decompression was negative [94].

3.5. **Trial Overlap.** Though nimodipine has demonstrated mortality and functional outcome benefit in SAH [4–6, 8, 110], it has shown no benefit in cardiac arrest trials [64, 65, 67]. Similarly, intracisternal thrombolysis showed some benefit in reducing delayed cerebral ischemia and infarction after SAH [36, 38], but intraavenous tenecteplase showed no long-term benefit and, in fact, increased intracranial hemorrhage after cardiac arrest [69, 70]. Neither magnesium [53, 54, 81–85] nor intensive insulin [59, 87] has proven beneficial after SAH or cardiac arrest. Though hypothermia [88, 89] has been the single most effective treatment for cardiac arrest (the number needed to treat to prevent one death is 7 and the number needed to treat to produce favorable neurological outcome is 6), it has not proven useful in the context of aneurysm surgery after SAH [60]. There is little mechanistic overlap in ongoing randomized, controlled trials of SAH and cardiac arrest patients.

4. **Discussion**

In this paper, a direct comparison is made between randomized, controlled clinical trials that evaluate mortality or neurologic outcome after SAH and cardiac arrest. Though 28% of SAH studies showed some neurologic outcome benefit in the intervention group, only nimodipine [4–6, 8, 110], fasudil [57, 58], and endovascular coiling [29–31] have been found to consistently improve outcome in multiple, multicenter randomized controlled trials. Smaller studies [8, 41, 58], single center [21, 44], or phase II safety and feasibility studies [13, 25, 45] have shown outcome benefit, but still require larger efficacy trials before integration into standard practice. Among cardiac arrest trials, only mild therapeutic hypothermia has been shown to improve both mortality and neurologic outcome [88, 89]. Little overlap in trial results or mechanisms of study was identified in these different patient populations.

Methodological differences in the timing, duration, neurologic severity, and outcomes studied may explain some of the differences in trial results between SAH and cardiac arrest populations. First, the timing of intervention for SAH and cardiac arrest trials is quite different. With the exception of aneurysm repair and aneurysm rebleeding trials (some of which were carried out in the era of delayed surgical treatment), the vast majority of SAH trials focus on the delayed cerebral ischemia period. Conversely, all cardiac arrest trials are directed at intervening against early brain injury. The difference in time frames studied may explain, in part, the variable results for mild therapeutic hypothermia in each population. Unlike the cardiac arrest trials, which applied hypothermia either prior to ED arrival [88] or within a median of 105 minutes from return of spontaneous circulation (ROSC) [89] for a duration of 12–24 hours, hypothermia was applied in the IHAST trial at a median of two days from SAH onset and only for a brief time (median 5–6 hours) [60]. Second, patient selection may result in variable trial results for hypothermia. For example, hypothermia for cardiac arrest was used for comatose survivors, while relatively neurologically intact patients (WFNS I–III) were studied in the IHAST trial. Finally, outcome measures differ in the cardiac arrest and SAH literature. Many cardiac trials measure 30-day or discharge mortality or neurologic outcome, while SAH trials measure outcomes from 3 months to 1 year. Though the majority of cardiac arrest trials measure neurologic outcome using the Pittsburgh cerebral performance scale, while SAH trials utilize the Glasgow outcome scale or modified Rankin scale, all of these scales are very similar and provide gross estimates of disability. Despite the aforementioned methodological differences, certain interventions, such as magnesium and intensive insulin, have not proven effective in either population.

Another reason for variable outcome in clinical trials may be due to pathophysiological differences in SAH and cardiac arrest. Though early brain injury in SAH may mechanistically mirror the cascade of injury occurring after cardiac arrest, SAH differs from cardiac arrest in that it is not a monophasic disease. Break down of blood products initiates a distinctive series of delayed clinical events that characteristically can lead to ischemia or infarction between SAH days 3–14. The fact that nimodipine has been so successful in SAH trials, but shown no effect at similar doses in cardiac arrest trials suggests it is acting on a distinct pathway. Indeed, the absolute risk reduction for poor outcome after SAH in a meta-analysis of 16 trials of nimodipine is 5.3% with a number needed to treat for benefit of 19 [III]. No such signal for benefit was seen in cardiac arrest trials [64, 65, 67]. The mechanism of beneficial effect of nimodipine in SAH has been widely debated and may be related to its effect on fibrinolysis [12], spreading cortical depression [13], or excitotoxicity. Though nimodipine improves ischemic neurological deficits by clinical criteria and CT-documented infarction (with a pooled relative risks of 0.66 (95% CI 0.59–0.75) and 0.78 (95% CI 0.70–0.87), resp.) [III], it has little effect on angiographic vasospasm or cerebral blood flow [4, 5]. The corollary to this observation is that interventions that improve angiographic vasospasm, such as clazosentan, do not necessarily improve cerebral infarction or outcome [49, 50, 114, 115]. While angiographic vasospasm seems to be related to infarction [116], other mechanisms may play a role in neurological deficits, cerebral infarction, and outcome. Such pathophysiological differences may make extrapolation of results from cardiac arrest trials to an SAH population problematic. Indeed, delayed cerebral ischemia (DCI) may blunt the positive effect of hypothermia on early brain injury. Further animal research may better identify mechanistic differences of early brain injury in cardiac arrest and SAH.

Despite a second wave of neurological injury in SAH, poor-grade (Hunt Hess 4-5) SAH patients, who are at higher risk for secondary neurological injury, still have comparable, if not better, outcomes compared to cardiac arrest patients who are not cooled. Among Hunt-Hess grade 4-5 patients, the 12-month mortality rate with aggressive treatment is 43%, while 40% had no or slight-moderate disability (mRS 0–3).
By comparison, the 6-month death rate in the control (nonhypothermia) group of the HACA trial was 55%, while good neurologic outcome (defined as Pittsburgh cerebral performance scale 1-2; good outcome or moderate disability) occurred in 26–39% [88, 89]. We have additionally shown that DCI does not predict mortality after SAH with aggressive vasospasm treatment, while early brain injury (measured by Hunt-Hess grade) does [1]. Thus, despite secondary neurologic insults and delayed cerebral ischemia risk, poor-grade SAH patients do at least as well as normothermic cardiac arrest patients, who may face risks to survival and functional outcome related to the underlying cause of the cardiac arrest. Also, the median age of cardiac arrest patients tends to be older than SAH patients, which may also explain why even the sickest SAH patients have relatively good outcomes by comparison. If nihilism can be overcome in the management of poor-grade SAH patients, the early application of mild therapeutic hypothermia may improve outcomes further.

There are some limitations to this review that should be mentioned. A medical librarian was not used and only MEDLINE/PubMed and clinicaltrials.gov were used to identify literature for review. An Embase search was not performed. Additionally, an exhaustive search for all neurologic outcome based RCTs was not performed, rather only English studies in humans were included.

In conclusion, while the mechanisms of early brain injury after SAH and cardiac arrest may be similar, the preponderance of SAH clinical trials do not focus on interventions addressing early brain injury. Clinical trials in SAH assessing interventions that have proven successful in the cardiac arrest literature, such as early mild therapeutic hypothermia, are warranted.

References

[1] J. A. Frontera, A. Fernandez, J. M. Schmidt et al., “Defining vasospasm after subarachnoid hemorrhage: what is the most clinically relevant definition?” Stroke, vol. 40, no. 6, pp. 1963–1968, 2009.

[2] K. E. Wartenberg, J. M. Schmidt, J. Claassen et al., “Impact of medical complications on outcome after subarachnoid hemorrhage,” Critical Care Medicine, vol. 34, no. 3, pp. 617–623, 2006.

[3] G. S. Allen, H. S. Ahn, T. I. Preziosi et al. et al., “Cerebral arterial spasm–a controlled trial of nimodipine in patients with subarachnoid hemorrhage,” The New England Journal of Medicine, vol. 308, no. 11, pp. 619–624, 1983.

[4] K. C. Petruk, M. West, G. Mohr et al., “Nimodipine treatment in poor-grade aneurysm patients. Results of a multicenter double-blind placebo-controlled trial,” Journal of Neurosurgery, vol. 68, no. 4, pp. 505–517, 1988.

[5] E. Mee, D. Dorrance, D. Lowe, and G. Neil-Dwyer, “Controlled study of nimodipine in aneurysm patients treated early after subarachnoid hemorrhage,” Neurosurgery, vol. 22, no. 3, pp. 484–491, 1988.

[6] J. D. Pickard, G. D. Murray, R. Illingworth et al., “Effect of oral nimodipine on cerebral infarction and outcome after subarachnoid haemorrhage: British aneurysm nimodipine trial,” British Medical Journal, vol. 298, no. 6674, pp. 636–642, 1989.

[7] J. M. Gilbsach, H. J. Reulen, B. Ljunggren et al., “Early aneurysm surgery and preventive therapy with intravenously administered nimodipine: a multicenter, double-blind, dose-comparison study,” Neurosurgery, vol. 26, no. 3, pp. 458–464, 1990.

[8] J. Ohman, A. Servo, and O. Heiskanen, “Long-term effects of nimodipine on cerebral infarcts and outcome after aneurysmal subarachnoid hemorrhage and surgery,” Journal of Neurosurgery, vol. 74, no. 1, pp. 8–13, 1991.

[9] V. Soppi, P. N. Karmanakos, T. Koivisto et al., “A randomized outcome study of enteral versus intravenous nimodipine in 171 patients after acute aneurysmal subarachnoid hemorrhage,” World Neurosurgery, vol. 78, no. 1-2, pp. 101–109, 2012.

[10] E. C. Haley Jr., N. F. Kassell, and J. C. Torner, “A randomized trial of nicardipine in subarachnoid hemorrhage: angiographic and transcranial Doppler ultrasound results. A report of the cooperative aneurysm study,” Journal of Neurosurgery, vol. 78, no. 4, pp. 548–553, 1993.

[11] E. C. Haley Jr., N. F. Kassell, and J. C. Torner, “A randomized controlled trial of high-dose intravenous nicardipine in aneurysmal subarachnoid hemorrhage. A report of the cooperative aneurysm study,” Journal of Neurosurgery, vol. 80, no. 5, pp. 537–547, 1994.

[12] E. C. Haley Jr., N. F. Kassell, J. C. Torner, L. L. Truskowski, and T. P. Germanson, “A randomized trial of two doses of nicardipine in aneurysmal subarachnoid hemorrhage: a report of the cooperative aneurysm study,” Journal of Neurosurgery, vol. 90, no. 2, pp. 788–796, 1999.

[13] M. Barth, H. H. Capelle, S. Weidauer et al., “Effect of nicardipine prolonged-release implants on cerebral vasospasm and clinical outcome after severe aneurysmal subarachnoid hemorrhage: a prospective, randomized, double-blind phase IIa study,” Stroke, vol. 38, no. 2, pp. 330–336, 2007.

[14] H. Fostad, A. Forsell, B. Liliequist, and M. Schannong, “Antifibrinolysis with tranexamic acid in aneurysmal subarachnoid hemorrhage: a consecutive controlled clinical trial,” Neurosurgery, vol. 8, no. 2, pp. 158–165, 1981.

[15] U. M. Chowdhary and K. Sayed, “Comparative clinical trial of epsilon amino-caproic acid and tranexamic acid in the prevention of early recurrence of subarachnoid haemorrhage,” Journal of Neurology, Neurosurgery and Psychiatry, vol. 44, no. 9, pp. 810–813, 1981.

[16] M. Vermeulen, K. W. Lindsay, G. D. Murray et al. et al., “Antifibrinolytic treatment in subarachnoid hemorrhage,” The New England Journal of Medicine, vol. 311, no. 7, pp. 432–437, 1984.

[17] Y. Roos, “Antifibrinolytic treatment in subarachnoid hemorrhage: a randomized placebo-controlled trial. STAR Study Group,” Neurology, vol. 54, no. 1, pp. 77–82, 2000.

[18] J. Hillman, S. Fridriksson, O. Nilsson, Z. Yu, H. Saveland, and T. P. Germanson, “A randomized trial of two doses of nicardipine in aneurysmal subarachnoid hemorrhage: a prospective randomized study,” Journal of Neurosurgery, vol. 97, no. 4, pp. 771–778, 2002.

[19] I. Saito, T. Asano, and C. Ochiai, “A double-blind clinical comparison study,” Neurosurgery, vol. 80, no. 4, pp. 537–547, 1993.

[20] T. Ohta, H. Kikuchi, K. Hashi, and Y. Kudo, “Nizofenone administered nimodipine: a multicenter, double-blind, dose-comparison study,” Neurosurgery, vol. 26, no. 3, pp. 458–464, 1990.

[21] A. Munakata, H. Ohkuma, T. Nakano, N. Shimamura, K. Asano, and M. Naraoka, “Effect of a free radical scavenger, edaravone,
in the treatment of patients with aneurysmal subarachnoid hemorrhage," *Neurosurgery*, vol. 64, no. 3, pp. 423–428, 2009.

[22] H. Yoneda, S. Shirao, J. Nakagawara, K. Ogasawara, T. Tomi-naga, and M. Suzuki, "A prospective, multicenter, randomized study of the efficacy of eicosapentaenoic acid for cerebral vasospasm: the EVAS study," *World Neurosurgery*, 2012.

[23] M. D. Hill, R. H. Martin, D. Mikulis et al. et al., "Safety and efficacy of NA-1 in patients with iatrogenic stroke after endovascu-lar aneurysm repair (ENACT): a phase 2, randomised, doubleblind, placebo-controlled trial," *The Lancet Neurology*, vol. 11, no. 11, pp. 942–950, 2012.

[24] J. R. Lynch, H. Wang, M. J. McGirt et al. et al., "Simvastatin reduces vasospasm after aneurysmal subarachnoid hemorrhage: results of a pilot randomized clinical trial," *Stroke*, vol. 36, no. 9, pp. 2024–2026, 2005.

[25] M. Y. Tseng, M. Czosnyka, H. Richards, J. D. Pickard, and P. J. Kirkpatrick, "Effects of acute treatment with pravastatin on cerebral vasospasm, autoregulation, and delayed ischemic deficits after aneurysmal subarachnoid hemorrhage: a phase II randomised placebo-controlled trial," *Stroke*, vol. 36, no. 8, pp. 1627–1632, 2005.

[26] S. H. Y. Chou, E. E. Smith, N. Badjatia et al. et al., "A randomized, double-blind, placebo-controlled pilot study of simvastatin in aneurysmal subarachnoid hemorrhage," *Stroke*, vol. 39, no. 10, pp. 2891–2893, 2008.

[27] M. D. Vergouwen, J. C. Meijers, R. B. Geskus et al. et al., "Biologic effects of simvastatin in patients with aneurysmal subarachnoid hemorrhage: a double-blind, placebo-controlled randomised trial," *Journal of Cerebral Blood Flow and Metabolism*, vol. 29, no. 8, pp. 1444–1453, 2009.

[28] J. Ohman and O. Heiskanen, "Timing of operation for ruptured supratentorial aneurysms: a prospective randomized study," *Journal of Neurosurgery*, vol. 70, no. 1, pp. 55–60, 1989.

[29] A. Molyneux, R. Kerr, I. Stratton et al. et al., "International subarachnoid aneurysm trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised trial," *The Lancet*, vol. 360, no. 9342, pp. 1267–1274, 2002.

[30] A. J. Molyneux, R. S. Kerr, L. M. Yu et al. et al., "International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised comparison of effects on survival, dependency, seizures, rebleeding, subgroups, and aneurysm occlusion," *The Lancet*, vol. 366, no. 9488, pp. 809–817, 2005.

[31] C. G. McDougall, R. F. Spetzler, J. M. Zabramski et al. et al., "The barrow ruptured aneurysm trial," *Journal of Neurosurgery*, vol. 116, no. 1, pp. 135–144, 2012.

[32] N. F. Kassell, E. C. Haley Jr., C. Apperson-Hansen, and W. M. Alves, "Randomized, double-blind, vehicle-controlled trial of tirilazad mesylate in patients with aneurysmal subarachnoid hemorrhage: a cooperative study in Europe, Australia, and New Zealand," *Journal of Neurosurgery*, vol. 84, no. 2, pp. 221–228, 1996.

[33] E. C. Haley Jr., N. F. Kassell, C. Apperson-Hansen, M. H. Maile, and W. M. Alves, "A randomized, double-blind, vehiclecontrolled trial of tirilazad mesylate in patients with aneurysmal subarachnoid hemorrhage: a cooperative study in North Amer-ica," *Journal of Neurosurgery*, vol. 86, no. 3, pp. 467–474, 1997.

[34] G. Lanzino, N. F. Kassell, N. W. C. Dorsch et al. et al., "Doubleblind, randomized, vehicle-controlled study of high-dose tirilazad mesylate in women with aneurysmal subarachnoid hemorrhage—part I: a cooperative study in Europe, Australia, New Zealand, and South Africa," *Journal of Neurosurgery*, vol. 90, no. 6, pp. 1011–1017, 1999.

[35] G. Lanzino and N. F. Kassell, "Double-blind, randomized, vehicle-controlled study of high-dose tirilazad mesylate in women with aneurysmal subarachnoid hemorrhage—part II: a cooperative study in North America," *Journal of Neurosurgery*, vol. 90, no. 6, pp. 1018–1024, 1999.

[36] V. Seifert, D. Stolke, M. Zimmermann, and A. Feldges, "Preven-tion of delayed ischaemic deficits after aneurysmal subarachnoaid haemorrhage by intrathecal bolus injection of tissue plasminogen activator (rTPA). A prospective study," *Acta Neu-rochirurgica*, vol. 128, no. 1–4, pp. 137–143, 1994.

[37] J. M. Findlay, "A randomized trial of intraoperative, intracis-ternal tissue plasminogen activator for the prevention of vasospasm," *Neurosurgery*, vol. 37, no. 5, pp. 1026–1027, 1995.

[38] T. Yamamoto, T. Esaki, Y. Nakao, and K. Morii, "Efficacy of lowdose tissue-plasminogen activator intracisternal administration for the prevention of cerebral vasospasm after subarachnoid hemorrhage," *World Neurosurgery*, vol. 73, no. 6, pp. 675–682, 2010.

[39] M. D. Shaw, P. M. Foy, M. Conway et al. et al., "Dipyridamole and postoperative ischemic deficits in aneurysmal subarachnoid hemorrhage," *Journal of Neurosurgery*, vol. 63, no. 5, pp. 699–703, 1985.

[40] W. M. van den Bergh, A. Algra, S. M. D. Mees, F. van Kooten, C. M. Dirven, J. van Gijn et al. et al., "Randomized controlled trial of acetylsalicylic acid in aneurysmal subarachnoid hemorrhage: the MASH study," *Stroke*, vol. 37, no. 9, pp. 2326–2330, 2006.

[41] S. Suzuki, T. Sayama, T. Nakamura et al. et al., "Cilostazol improves outcome after subarachnoid hemorrhage: a preliminary report," *Cerebrovascular Diseases*, vol. 32, no. 1, pp. 89–93, 2011.

[42] D. Hasan, K. W. Lindsay, E. F. M. Wijdicks et al. et al., "Effect of fludrocortisone acetate in patients with subarachnoid hemor-rhage," *Stroke*, vol. 20, no. 9, pp. 1156–1161, 1989.

[43] Y. Katayama, J. Haraoaka, H. Hirabayashi et al. et al., "A randomized controlled trial of hydrocortisone against hyponatremia in patients with aneurysmal subarachnoid hemorrhage," *Stroke*, vol. 38, no. 8, pp. 2373–2375, 2007.

[44] P. Gomis, J. P. Graftieaux, R. Sercombe, D. Hettiler, B. Scherpeereel, and P. Rousseaux, "Randomized, double-blind, placebocontrolled pilot trial of high-dose methylprednisolone in aneurysmal subarachnoid hemorrhage," *Journal of Neurosurgery*, vol. 112, no. 3, pp. 681–688, 2010.

[45] M. Y. Tseng, P. J. Hutchinson, H. K. Richards et al. et al., "Acute systemic erythropoietin therapy to reduce delayed ischemic deficits following aneurysmal subarachnoid hemorrhage: a phase II randomized, double-blind, placebo-controlled trial: clinical article," *Journal of Neurosurgery*, vol. 111, no. 1, pp. 171–180, 2009.

[46] A. M. Naidech, A. Shaibani, R. K. Garg et al. et al., "Prospective, randomized trial of higher goal hemoglobin after subarachnoid hemorrhage," *Neurocritical Care*, vol. 13, no. 3, pp. 313–320, 2010.

[47] J. I. Suarez, R. H. Martin, E. Calvillo et al. et al., "The albumin in subarachnoid hemorrhage (ALISAH) multicenter pilot clinical trial: safety and neurologic outcomes," *Stroke*, vol. 43, no. 3, pp. 683–690, 2012.

[48] B. A. Bell, "Effect of calcitonin-gene-related peptide in patients with delayed postoperative cerebral ischaemia after aneurysmal subarachnoid haemorrhage," *The Lancet*, vol. 339, no. 8797, pp. 831–834, 1992.
[49] R. L. Macdonald, R. T. Higashida, E. Keller et al., “Clazosentan, an endothelin receptor antagonist, in patients with aneurysmal subarachnoid haemorrhage undergoing surgical clipping: a randomised, double-blind, placebo-controlled phase 3 trial (CONSCIOUS-2),” The Lancet Neurology, vol. 10, no. 7, pp. 618–625, 2011.

[50] R. L. Macdonald, R. T. Higashida, E. Keller et al. et al., “Randomized trial of clazosentan in patients with aneurysmal subarachnoid hemorrhage undergoing endovascular coiling,” Stroke, vol. 43, no. 6, pp. 1463–1469, 2012.

[51] L. Lennihan, S. A. Mayer, M. E. Fink et al. et al., “Effect of hypertensive therapy on cerebral blood flow after subarachnoid hemorrhage: a randomized controlled trial,” Stroke, vol. 31, no. 2, pp. 383–391, 2000.

[52] A. Egge, K. Waterloo, H. Sjøholm, T. Solberg, T. Ingebrigtsen, and B. Romner, “Prophylactic hyperdynamic postoperative fluid therapy after aneurysmal subarachnoid hemorrhage: a clinical, prospective, randomized, controlled study,” Neurosurgery, vol. 49, no. 3, pp. 593–606, 2001.

[53] G. K. C. Wong, W. S. Poon, M. T. V. Chan et al. et al., “Intravenous magnesium sulphate for aneurysmal subarachnoid hemorrhage (IMASH): a randomized, double-blind, placebo-controlled, multicenter phase III trial,” Stroke, vol. 41, no. 5, pp. 921–926, 2010.

[54] S. M. D. Mees, A. Algra, W. P. Vandertop et al. et al., “Magnesium for aneurysmal subarachnoid haemorrhage (MASH-2): a randomised placebo-controlled trial,” The Lancet, vol. 380, no. 9836, pp. 44–49, 2012.

[55] P. Walter, G. Neil-Dwyer, and J. M. Cruickshank, “Beneficial effects of adrenergic blockade in patients with subarachnoid haemorrhage,” The British Medical Journal, vol. 284, no. 6330, pp. 1661–1664, 1982.

[56] M. Zwienenberg-Lee, J. Hartman, N. Rudisill et al. et al., “Effect of prophylactic transluminal balloon angioplasty on cerebral vasospasm and outcome in patients with fisher grade III subarachnoid hemorrhage: results of a phase II multicenter, randomized, clinical trial,” Stroke, vol. 39, no. 6, pp. 1759–1765, 2008.

[57] M. Shibuya, Y. Suzuki, K. Sugita et al. et al., “Effect of AT877 on cerebral vasospasm after aneurysmal subarachnoid hemorrhage: results of a prospective placebo-controlled double-blind trial,” Journal of Neurosurgery, vol. 76, no. 4, pp. 571–577, 1992.

[58] J. Zhao, D. Zhou, J. Guo et al. et al., “Efficacy and safety of fusidil in patients with subarachnoid hemorrhage: final results of a randomized trial of fusidil versus nimodipine,” Neurologia Medico-Chirurgica, vol. 51, no. 10, pp. 679–683, 2011.

[59] F. Bilotta, A. Spinelli, E. Giovannini, A. Doriano, R. Delfini, and G. Rosa, “The effect of intensive insulin therapy on infection rate, vasospasm, neurologic outcome, and mortality in neurointensive care unit after intracranial aneurysm clipping in patients with acute subarachnoid hemorrhage: a randomized prospective pilot trial,” Journal of Neurosurgical Anesthesiology, vol. 19, no. 3, pp. 156–160, 2007.

[60] M. M. Todd, B. J. Hindman, W. R. Clarke, and J. C. Torner, “Mild intraoperative hypothermia during surgery for intracranial aneurysm,” The New England Journal of Medicine, vol. 352, no. 2, pp. 135–145, 2005.

[61] E. Grote and W. Hassler, “The critical first minutes after subarachnoid hemorrhage,” Neurosurgery, vol. 22, no. 4, pp. 654–661, 1988.

[62] F. A. Sehba, G. Mostafa, V. Friedrich Jr., and J. B. Bederson, “Acute microvascular platelet aggregation after subarachnoid hemorrhage,” Journal of Neurosurgery, vol. 102, no. 6, pp. 1094–1100, 2005.

[63] F. A. Sehba and J. B. Bederson, “Mechanisms of acute brain injury after subarachnoid hemorrhage,” Neurological Research, vol. 28, no. 4, pp. 381–398, 2006.

[64] M. Forsman, H. P. Aarseth, H. K. Nordby, A. Skulberg, and P. A. Steen, “Effects of nimodipine on cerebral blood flow and cerebrospinal fluid pressure after cardiac arrest: correlation with neurologic outcome,” Anesthesia and Analgesia, vol. 68, no. 4, pp. 436–443, 1989.

[65] R. O. Roine, S. Kajaste, and M. Kaste, “Neuropsychological sequelae of cardiac arrest,” The Journal of the American Medical Association, vol. 269, no. 2, pp. 237–242, 1992.

[66] Brain Resuscitation Clinical Trial II Study Group, “A randomized clinical study of a calcium-entry blocker (lidoflazine) in the treatment of comatose survivors of cardiac arrest,” The New England Journal of Medicine, vol. 324, no. 18, pp. 1225–1231, 1991.

[67] R. O. Roine, M. Kaste, A. Kinnunen, P. Nikki, S. Sarna, and S. Kajaste, “Nimodipine after resuscitation from out-of-hospital ventricular fibrillation. A placebo-controlled, double-blind, randomized trial,” The Journal of the American Medical Association, vol. 264, no. 24, pp. 3171–3177, 1990.

[68] M. S. Damian, D. Ellenberg, R. Gildemeister et al., “Coenzyme Q10 combined with mild hypothermia after cardiac arrest: a preliminary study,” Circulation, vol. 110, no. 19, pp. 3011–3016, 2004.

[69] D. M. Fatovich, G. J. Dobb, and R. A. Clagston, “A pilot randomised trial of thrombolysis in cardiac arrest (the TICA trial),” Resuscitation, vol. 61, no. 3, pp. 309–313, 2004.

[70] B. W. Böttiger, H. R. Arntz, D. A. Chamberlain et al., “Thrombolysis during resuscitation for out-of-hospital cardiac arrest,” The New England Journal of Medicine, vol. 359, no. 25, pp. 2651–2662, 2008.

[71] S. D. Mentzelopoulos, S. G. Zakythinos, M. Tzoufi et al., “Vasopressin, epinephrine, and corticosteroids for in-hospital cardiac arrest,” Archives of Internal Medicine, vol. 169, no. 1, pp. 15–24, 2009.

[72] C. G. Brown, D. R. Martin, P. E. Pepe et al. et al., “A comparison of standard-dose and high-dose epinephrine in cardiac arrest outside the hospital. The multicenter high-dose epinephrine study group,” The New England Journal of Medicine, vol. 327, no. 15, pp. 1051–1055, 1992.

[73] C. Choux, P. Y. Gueugniaud, A. Barbieux et al., “Standard doses versus repeated high doses of epinephrine in cardiac arrest outside the hospital,” Resuscitation, vol. 29, no. 1, pp. 3–9, 1995.

[74] W. D. Patrick, J. Freedman, T. McEwen, R. B. Licht, L. Ludvig, and D. Roberts, “A randomized, double-blind comparison of methoxamine and epinephrine in human cardiopulmonary arrest,” The American Journal of Respiratory and Critical Care Medicine, vol. 152, no. 2, pp. 519–523, 1995.

[75] K. H. Lindner, B. Dirks, H. U. Strohmenger, A. W. Prengel, and S. Kajaste, “Nimodipine after resuscitation from out-of-hospital ventricular fibrillation,” The Lancet, vol. 349, no. 9051, pp. 535–537, 1997.

[76] B. W. Sherman, M. A. Munger, G. E. Foulke, W. F. Rutherford, and E. A. Panacek, “High-dose versus standard-dose epinephrine treatment of cardiac arrest after failure of standard therapy,” Pharmacotherapy, vol. 17, no. 2, pp. 242–247, 1997.

[77] P. Y. Gueugniaud, P. Mols, P. Goldstein et al., “A comparison of repeated high doses and repeated standard doses of epinephrine...” The New England Journal of Medicine, vol. 327, no. 2, pp. 242–247, 1992.
for cardiac arrest outside the hospital,” *The New England Journal of Medicine*, vol. 339, no. 22, pp. 1595–1601, 1998.

[78] I. G. Stiell, P. C. Hébert, G. A. Wells et al., “Vasopressin versus epinephrine for inhospital cardiac arrest: a randomised controlled trial,” *The Lancet*, vol. 358, no. 9276, pp. 105–109, 2001.

[79] V. Wenzel, A. C. Krismer, H. R. Arntz, H. Sitter, K. H. Stadlbauer, and K. H. Lindner, “A comparison of vasopressin and epinephrine for out-of-hospital cardiopulmonary resuscitation,” *The New England Journal of Medicine*, vol. 350, no. 2, pp. 105–113, 2004.

[80] P. Y. Gueugniaud, J. S. David, E. Chanzy et al. et al., “Vasopressin and epinephrine vs. epinephrine alone in cardiopulmonary resuscitation,” *The New England Journal of Medicine*, vol. 359, no. 1, pp. 21–30, 2008.

[81] M. C. Thel, A. L. Armstrong, S. E. McNulty, R. M. Califf, and C. M. O’Connor, “Randomised trial of magnesium in in-hospital cardiac arrest,” *The Lancet*, vol. 350, no. 9087, pp. 1272–1276, 1997.

[82] D. M. Fatovich, D. A. Prentice, and G. J. Dobb, “Magnesium in cardiac arrest (the magic trial),” *Resuscitation*, vol. 35, no. 3, pp. 237–241, 1997.

[83] J. Allegra, R. Lavery, R. Cody et al., “Magnesium sulfate in the treatment of refractory ventricular fibrillation in the prehospital setting,” *Resuscitation*, vol. 49, no. 3, pp. 245–249, 2001.

[84] T. B. Hassan, C. Jagger, and D. B. Barnett, “A randomised trial to investigate the efficacy of magnesium sulphate for refractory ventricular fibrillation,” *Emergency Medicine Journal*, vol. 19, no. 1, pp. 57–62, 2002.

[85] W. T. Longstreth Jr., C. E. Fahrenbruch, M. Olsufka, T. R. Walsh, M. K. Copass, and L. A. Cobb, “Randomized clinical trial of magnesium, diazepam, or both after out-of-hospital cardiac arrest,” *Neurology*, vol. 59, no. 4, pp. 506–514, 2002.

[86] W. T. Longstreth Jr., M. K. Copass, L. K. Dennis, M. E. Rauch-Matthews, M. S. Stark, and L. A. Cobb, “Intravenous glucose after out-of-hospital cardiopulmonary arrest: a community-based randomized trial,” *Neurology*, vol. 43, no. 12 I, pp. 2534–2541, 1993.

[87] T. Oksanen, M. B. Skrifvars, T. Varpula et al., “Strict versus moderate glucose control after resuscitation from ventricular fibrillation,” *Intensive Care Medicine*, vol. 33, no. 12, pp. 2093–2100, 2007.

[88] S. A. Bernard, T. W. Gray, M. D. Buist et al., “Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia,” *The New England Journal of Medicine*, vol. 346, no. 8, pp. 557–563, 2002.

[89] The Hypothermia after Cardiac Arrest Study Group, “Mild therapeutic hypothermia to improve neurologic outcome after cardiac arrest,” *The New England Journal of Medicine*, vol. 346, no. 8, pp. 549–556, 2002.

[90] F. Kim, M. Olsufka, W. T. Longstreth Jr. et al., “Pilot randomized clinical trial of prehospital induction of mild hypothermia in out-of-hospital cardiac arrest patients with a rapid infusion of 4°C normal saline,” *Circulation*, vol. 115, no. 24, pp. 3064–3070, 2007.

[91] A. Kämäräinen, I. Virkkunen, J. Tenhunen, A. Yli-Hankala, and T. Silfvast, “Prehospital therapeutic hypothermia for comatose survivors of cardiac arrest: a randomized controlled trial,” *Acta Anaesthesiologica Scandinavica*, vol. 53, no. 7, pp. 900–907, 2009.

[92] M. Castrén, P. Nordberg, L. Svensson et al., “Intra-arrest transnasal evaporative cooling: a randomized, prehospital, multicenter study (PRINCE: pre-ROSCIntraNasal cooling effectiveness),” *Circulation*, vol. 122, no. 7, pp. 729–736, 2010.

[93] T. J. Cohen, B. G. Goldner, P. C. Maccaro et al., “A comparison of active compression-decompression cardiopulmonary resuscitation with standard cardiopulmonary resuscitation for cardiac arrests occurring in the hospital,” *The New England Journal of Medicine*, vol. 329, no. 26, pp. 1918–1921, 1993.

[94] I. G. Stiell, P. C. Hébert, G. A. Wells et al., “The Ontario trial of active compression-decompression cardiopulmonary resuscitation for in-hospital and prehospital cardiac arrest,” *The Journal of the American Medical Association*, vol. 275, no. 18, pp. 1417–1423, 1996.

[95] A. Hallstrom, L. Cobb, E. Johnson, and M. Copass, “Cardiopulmonary resuscitation by chest compression alone or with mouth-to-mouth ventilation,” *The New England Journal of Medicine*, vol. 342, no. 21, pp. 1546–1553, 2000.

[96] C. Bertrand, F. Hemery, P. Carli et al., “Constant flow insufflation of oxygen as the sole mode of ventilation during out-of-hospital cardiac arrest,” *Intensive Care Medicine*, vol. 32, no. 6, pp. 843–851, 2006.

[97] L. Svensson, K. Bohl, M. Castrén et al., “Compression-only CPR or standard CPR in out-of-hospital cardiac arrest,” *The New England Journal of Medicine*, vol. 363, no. 5, pp. 434–442, 2010.

[98] T. D. Rea, C. Fahrenbruch, L. Culley et al., “CPR with chest compression alone or with rescue breathing,” *The New England Journal of Medicine*, vol. 363, no. 5, pp. 423–433, 2010.

[99] T. P. Auferheide, G. Nichol, T. D. Rea et al., “A trial of an impedance threshold device in out-of-hospital cardiac arrest,” *The New England Journal of Medicine*, vol. 365, no. 9, pp. 798–806, 2011.

[100] R. B. Abu-Laban, C. M. McIntyre, J. M. Christenson et al., “Aminophylline in bradyasystolic cardiac arrest: a randomised placebo-controlled trial,” *The Lancet*, vol. 367, no. 9522, pp. 1577–1584, 2006.

[101] B. E. Heradstveit, A. B. Guttmormsen, J. Langorgen et al., “Capillary leakage in post-cardiac arrest survivors during therapeutic hypothermia—a prospective, randomised study,” *Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine*, vol. 18, article 29, 2010.

[102] Brain Resuscitation Clinical Trial I Study Group, “Randomized clinical study of thiopental loading in comatose survivors of cardiac arrest,” *The New England Journal of Medicine*, vol. 314, no. 7, pp. 397–403, 1986.

[103] H. A. Stueven, B. M. Thompson, C. Aprahamian, and D. J. Tonsfeldt, “Calcium chloride: reassessment of use in asystole,” *Annals of Emergency Medicine*, vol. 13, no. 9, pp. 820–822, 1984.

[104] H. A. Stueven, B. Thompson, C. Aprahamian, D. J. Tonsfeldt, and E. H. Kastenson, “The effectiveness of calcium chloride in refractory electromechanical dissociation,” *Annals of Emergency Medicine*, vol. 14, no. 7, pp. 626–629, 1985.

[105] H. A. Stueven, B. Thompson, C. Aprahamian, D. J. Tonsfeldt, and E. H. Kastenson, “Lack of effectiveness of calcium chloride in refractory asystole,” *Annals of Emergency Medicine*, vol. 14, no. 7, pp. 630–632, 1985.

[106] T. Dybkiv, T. Strand, and P. A. Steen, “Buffer therapy during out-of-hospital cardiopulmonary resuscitation,” *Resuscitation*, vol. 29, no. 2, pp. 89–95, 1995.

[107] R. B. Vukmir and L. Katz, “Sodium bicarbonate improves outcome in prolonged prehospital cardiac arrest,” *American Journal of Emergency Medicine*, vol. 24, no. 2, pp. 156–161, 2006.
[108] I. Laurent, C. Adrie, C. Vinsonneau et al., “High-volume hemofiltration after out-of-hospital cardiac arrest: a randomized study,” *Journal of the American College of Cardiology*, vol. 46, no. 3, pp. 432–437, 2005.

[109] I. G. Stiell, G. Nichol, B. G. Leroux et al. et al., “Early versus later rhythm analysis in patients with out-of-hospital cardiac arrest,” *The New England Journal of Medicine*, vol. 365, no. 9, pp. 787–797, 2011.

[110] G. S. Allen, H. S. Ahn, T. J. Preziosi et al. et al., “Cerebral arterial spasm: a controlled trial of nimodipine in patients with subarachnoid hemorrhage,” *The New England Journal of Medicine*, vol. 308, no. 11, pp. 619–624, 1983.

[111] S. M. D. Mees, G. J. E. Rinkel, V. L. Feigin et al., “Calcium antagonists for aneurysmal subarachnoid hemorrhage,” *Stroke*, vol. 39, no. 2, pp. 514–515, 2008.

[112] Y. B. W. E. M. Roos, M. Levi, T. A. Carroll, L. F. M.Beenen, and M. Vermeulen, “Nimodipine increases fibrinolytic activity in patients with aneurysmal subarachnoid hemorrhage,” *Stroke*, vol. 32, no. 8, pp. 1860–1862, 2001.

[113] J. P. Dreier, K. Körner, N. Ebert et al., “Nitric oxide scavenging by hemoglobin or nitric oxide synthase inhibition by N-nitro-L-arginine induces cortical spreading ischemia when K+ is increased in the subarachnoid space,” *Journal of Cerebral Blood Flow and Metabolism*, vol. 18, no. 9, pp. 978–990, 1998.

[114] M. D. Vergouwen, A. Algra, and G. J. Rinkel, “Endothelin receptor antagonists for aneurysmal subarachnoid hemorrhage: a systematic review and meta-analysis update,” *Stroke*, vol. 43, no. 10, pp. 2671–2676, 2012.

[115] X. Wang, Y. M. Li, W. Q. Li, C. G. Huang, Y. C. Lu, and L. J. Hou, “Effect of clazosentan in patients with aneurysmal subarachnoid hemorrhage: a meta-analysis of randomized controlled trials,” *PloS ONE*, vol. 7, no. 10, Article ID e47778, 2012.

[116] R. W. Crowley, R. Medel, A. S. Dumont et al. et al., “Angiographic vasospasm is strongly correlated with cerebral infarction after subarachnoid hemorrhage,” *Stroke*, vol. 42, no. 4, pp. 919–923, 2011.

[117] J. Mocco, E. R. Ransom, R. J. Komotar et al., “Preoperative prediction of long-term outcome in poor-grade aneurysmal subarachnoid hemorrhage,” *Neurosurgery*, vol. 59, no. 3, pp. 529–538, 2006.