

2022

## Stroke Patient Outcomes When Fever Is Present

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**Stroke Patient Outcomes When Fever is Present**

A Scholarly Inquiry Paper  
Submitted to the Faculty  
of the Department of Nursing  
College of Nursing and Health Sciences  
of Winona State University

by  
Anthony L. P. Grant

In Partial Fulfillment of the Requirements  
For the Degree of  
Master of Science

1/27/2022

Winona State University



**COMPLETED SCHOLARLY INQUIRY PAPER APPROVAL FORM**

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RE: FACULTY ENDORSEMENT and FINAL REVIEW COMMITTEE

DATE: 01/27/2022

**SCHOLARLY INQUIRY PAPER TITLE:**

Stroke Patient Outcomes When Fever is Present

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**Date of Final Approval by Committee:** 01/27/2022

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## **ACKNOWLEDGEMENT**

### **Diane Forsyth**

Your guidance and supervision throughout this inquiry process has forever changed how I understand research. You have taught me a skill that will forever shape my clinical practice. Thank you for insight for I will be forever grateful.

### **Anne Loth**

The journey through this inquiry process has been both challenging and rewarding. Your support and belief in my abilities has been a source of strength that has helped me through this research process. Thank you for your undoubting encouragement and guidance.

### **Angela Grant**

To my wife, lifelong partner, and mother of my three special children. There are no words to describe how thankful I am for your support throughout this entire process. This would have not been achievable without you by my side. I am both blessed and eternally grateful to have you in my life. I cannot express this enough but thanks for everything you do.

## ABSTRACT

***Introduction to the Problem:*** Prescribers in the acute care setting differ in opinions with the role fever plays with stroke patient outcomes. This is evident by contrasting guideline recommendations and differing plan of care development amongst prescribers. This lack of clarity has led to the question; does fever affect stroke patient outcomes in that acute care setting.

***Supporting Literature:*** The research utilized for this inquiry was specific to both ischemic and hemorrhagic stroke patient outcomes when fever is present.

***Methods Used for Inquiry:*** An integrative literature review was conducted for this inquiry. A total of ninety articles were reviewed, with twenty-one selected. The literature review was conducted over material from the years 2000 to the present. The databases utilized to find the research for this inquiry included CINAHL, PubMed, and Cochrane libraries.

***Strength of Evidence:*** The strength of evidence utilized for this inquiry was a rating scheme of one to five. This inquiry included six systematic reviews or meta-analysis, one randomized controlled-trial, five prospective non-randomized trials, and nine retrospective comparative studies.

***Conclusion:*** Stroke patient outcomes were found to be significantly worse when fever is present. Diminished patient outcomes were found in both ischemic and hemorrhagic stroke populations. This was measured by poor functional outcomes, increased stroke severity, increased hospital length of stay, elevated pro-inflammatory markers, larger infarction volume, and larger hematoma volumes. The highest presence of fever was found in subarachnoid and intraventricular hemorrhage patient populations. Fever threshold was identified with a range from 37-38.5C. Treatment options for febrile stroke patients were inconclusive and further data is needed

to strengthen the argument for appropriate therapies. Additional research is needed regarding treatment intervention for fevers for stroke patients.

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## **Introduction**

### **Introduction to the Inquiry**

The introduction for this scholarly inquiry paper (SIP) contains several components. The inquiry analyzes patient outcomes in acute care post-stroke patient populations when fever is present. Background and rationale regarding the importance of this topic are discussed. The purpose or aim of this paper is included as well as the clinical question to the inquiry. Finally, methods used for the inquiry are discussed, summarizing the method used for this scholarly inquiry research paper.

Stroke patients account for a large number of hospital admissions each year in the United States. The Centers for Disease Control and Prevention (CDC) highlighted that every forty seconds someone suffers a stroke in the United States, and every four minutes an individual dies of stroke related illness (CDC, 2020). Stroke is the main cause of disability and the fifth leading cause of death in America (American Heart Association, 2020). Stroke care also comes with a high economic burden costing healthcare \$46 billion in 2014 and 2015 (CDC, 2020). Although, advances in research to improve patient outcomes have been identified, conflicting evidence still exists for patients who suffer a stroke.

### **Background and Rationale**

There are many intricacies to providing quality care to patients suffering from a stroke. Research has placed more emphasis on evidence-based care to stroke patients in the acute care settings. Stroke care guidelines have been established to guide treatments and plans of care for individuals who suffer from stroke. Grogan et al. (2019) found that when Canada adopted a standardized approach to stroke system care, there was a 15% reduction of inpatient hospital mortality rates. Various organizations, including the American Stroke Association (ASA) and

European Stroke Organization (ESO) have developed guidelines for inpatient treatment of strokes (Ntalos et al., 2015; Power et al., 2019).

The ASA and ESO guidelines have conflicting recommendations for the treatment of fever in post-stroke patient populations. The 2019 ASA treatment guidelines include the use of anti-pyretic medications when fever is greater than 38 degrees Celsius (Power et al., 2019). On the other hand, the ESO recommendations do not include anti-pyretic's and further discuss that treatment of fever has not shown benefit to functional outcome and/or survival (Ntalos et al. 2015). The conflicting treatment guidelines from both the ASA and ESO have highlighted the need for further exploration regarding stroke patient outcomes when fever is present. Conflicting plans of care and knowledge regarding stroke populations who develop fever are common in the acute care setting. The background to this dilemma is highlighted in the following case study noting the complexities of stroke care regarding fever management.

### **Case Study**

Mr. X is a 46-year-old male who suffered an aneurysmal subarachnoid hemorrhage with intraventricular extension. Typically, these patients are transferred to a comprehensive stroke facility with multiple specialties, including Neurosurgery and Neurologists specializing in individual stroke care. In addition, these facilities typically have a neurology intensive care unit and general neurology unit that provides specialty care to stroke patients. The goal of all stroke units is to provide evidence-based practice from all levels of care including the management of fever.

Mr. X, on admission, was confused to date, situation, and demonstrated mild aphasia with right-sided weakness and temperature of 99-degree Fahrenheit. The patient was intubated in the intensive care unit several hours after admission related to a decrease in his level of

consciousness and Glasgow Coma Scale rating of eight. The admitting team documented the fever in the history and physical note with a need to continue to monitor the plan of care. The patient had an aneurysm coiling on post bleed day two with no complications. The patient's fever continued to climb throughout the patient's admission to 102 degrees Fahrenheit on post bleed day three. Throughout the patient's care, the nursing staff continued to approach the admitting team regarding the temperatures and were repeatedly told the fever was not concerning. The lack of concern was also evident in prescribers' notes and orders that describe a 'continue monitoring' plan of care regarding the elevated temperatures.

Next, a second medical service was consulted to help manage Mr. X's plan of care. The second medical service placed immediate emphasis on the patient's fever. They discussed concerns that the fevers will directly affect Mr. X's outcome. The new service revised the plan of care involving scheduled antipyretic's, induced normothermia with cooling pads, and work-up for infection including blood, cerebral spinal fluid, sputum, and urinary cultures. The patient was discharged from the hospital one month later to a transitional care unit with significant neurological deficits and a Modified Rankin Score (mRS) of four. The drastic difference between prescribers suggests that further evidence is needed regarding stroke patient outcomes when fever is present.

### **Problem**

The problem for this inquiry is the lack of evidence regarding fever and stroke patient outcomes. Prescribers in the acute care setting are uncertain about stroke patient outcomes when fever is present. The conflicting recommendations between the AHA and ESO guidelines have furthered the divide amongst prescribers regarding the role fever plays on patient outcomes for those experiencing stroke. Post-stroke patients in the acute care settings face many challenges.

Understanding stroke patient outcomes when fever is present is necessary to achieving standardized care.

### **Purpose**

When fever is present, determining stroke patient outcomes will help providers prioritize fever in their treatment plans of care. This inquiry aims to identify stroke patient outcomes in the acute care setting when fever is present. This understanding will help providers enhance their knowledge base regarding stroke patient outcomes. In addition, it can enhance a common understanding between prescribers which will aid in standardized care of stroke patients when fever is present.

### **Question**

Does a fever affect outcomes in acute care post-stroke patient populations?

### **Methods Used for the Inquiry**

The methodological approach to this inquiry was an integrative literature review. This integrative literature review was comprehensively expanding through several platforms of research. The inquiry involved several steps, including formulating the research question, establishing inclusion criteria, selecting the literature, assessing the quality of the literature, analyzing and synthesizing the research, and disseminating the findings (Cronin et al., 2008). The objective was to identify the appropriate research for this inquiry and critically analyze the supportive evidence. The goal is to identify an evidence-based answer to the clinical question of this inquiry.

## **Literature Review**

### **Introduction**

The literature review section provides an introduction that describes the data abstraction process. It also notes how the literature was searched, and selection criteria utilized for this inquiry paper. The number of articles reviewed and utilized for the inquiry paper are listed in Appendix A. The synthesis of the literature will also be discussed regarding the heading and subheading format. Finally, the research studies utilized for this inquiry paper are listed in Appendix B.

### **Database Extraction Process**

The literature review database (see Appendix A) inclusion process included both ischemic stroke and intracerebral hemorrhage as well as both fever and patient outcomes. The article selection process was specific to patients 18 years of older who suffered an acute stroke, were hospitalized, and developed fever with patient outcome measures present. The databases search included CINAHL, Pub Med, and Cochrane library. All three databases produced a wealth of data regarding stroke, fever, and patient outcomes. An exhaustive research search and overlapping data were reached between the different databases. Bibliographies were also searched for articles included with this inquiry, which intensified the research efforts for pertinent data. A total of twenty-one articles were utilized for this inquiry. The search dates utilized for article selection were years 2000 to the present.

### **Synthesis of Literature Narrative**

The literature review narrative was discussed in sections related to the type of stroke researched. Three headings were created with the different types of stroke assessed. The sections were organized into research articles exclusive to ischemic stroke, intracerebral hemorrhage, or both ischemic stroke and intracerebral hemorrhage. The narrative was then further divided into

purpose, outcomes, and summary. Finally, each subheading narrative was grouped to commonalities of each article including outcome measures, study results, and level of evidence.

Headings were also created for both intervention outcomes with the treatment of fever in stroke patients and clinical guidelines reviewed for this inquiry. The rating system used to grade the level of evidence is provided at the end of Appendix B. The AGREE II tool was also utilized for clinical guideline appraisals, located in Appendices D and E. According to the research provided in Appendix B, stroke patients are often assessed using different functional scales for independence, outcome scores for stroke outcome, and stroke assessment scales for stroke severity. These stroke scales are listed in detail in Appendix E through H (JCHQM, 2018; McMillian et al., 2016; The Internet Stroke Center, 2021).

### **Combined Ischemic Stroke and Intracerebral Hemorrhage Studies**

***Purpose:*** Results from five studies (see Appendix B) assessed both ischemic stroke and intracerebral hemorrhage (ICH) in post-stroke patients related to fever. Greer et al. (2008) assessed the significance of the relationship between fever and outcome across the full range of neurological injury including stroke, and its effect on clinical, functional, and economic outcomes. Greer et al. (2008) identified several outcomes measured including mortality, mRS, intensive care unit (ICU) length of stay and hospital length of stay (LOS). The Joint Commission National Quality Measures (JCHQM) identifies the mRS as a measure for functional independence in stroke patients see Appendix E for mRS scale details (JCHQM, 2018). Similar to Greer et al. (2008), Middleton et al. (2018) utilized mRS as its outcome of measure in post stroke patients related to fever.

The study purpose of Middleton et al. (2018) was to examine an mRS at ninety days post-stroke to identify if fever contributes to decreased functional independence. Greer et al. (2008)

and Middleton et al. (2018) shared large patient sample sizes that display more robust support of outcomes measured. Kammergard et al. (2002) evaluated admission body temperature as an independent predictor of long-term prognosis. This study assessed the long-term impacts of fever, in which mortality was measured at three months and five years. This study is unique because it evaluated patient outcomes at five years. The studies in Appendix B have no primary outcome measures past eighteen months.

The mortality rate was a frequent outcome measure utilized in many of the studies reviewed. Saxena et al. (2015) assessed mortality outcomes concerning stroke patients who develop a fever. Their study inclusion criteria included both traumatic brain injury (TBI) and central nervous system (CNS) infection patient populations. This research study was large, including patient populations from two different countries. Saxena et al. (2015) assessed peak temps during the first twenty-four hours and assessed mortality as its outcome measures.

Medical complications are common with hospital admissions. The Agency for Healthcare and Quality (AHRQ) reported in 2014 for every 1,000 hospital admissions 90 hospital-acquired complications developed (AHRQ, 2018). The purpose of Rocco et al. (2007) was to determine what medical complications are the most frequent and how they influence stroke patient outcomes. Rocco et al. (2007) also aimed to identify how long patients should remain in a stroke unit to achieve improved patient outcomes. The American Heart Association (AHA) describes primary and comprehensive stroke centers as a format to provide specialized stroke care, which has been shown to improve outcomes and quality of care received (AHA, 2014). Therefore, Rocco et al.'s (2007) study was to identify how long patients need to remain in a stroke unit is important to better understand improved stroke patient outcomes.

**Outcomes:** There are several different ways to measure stroke patient outcomes and functionality. These measures include mortality, length of stay (LOS), Glasgow Outcome Scale, Barthel Index, and Canadian Stroke Scale. The stroke scales Barthel Index, Glasgow Outcome Scale, and Canadian Stroke Scale are located in Appendices G, H, and I. Greer et al. (2008) described length of stay with both ICU and hospital admission having the highest risk associated with fever in post-stroke patient populations; followed by mRS, mortality, Barthel Index, Canadian Stroke Scale and the Glasgow Outcome Scale. Geer et al. (2008) is a systematic review and meta-analysis that looked at multiple studies all with their own definitions of the outcomes described above. Greer et al. (2008) discussed that all of the outcome measures were found to be significant and that patient outcomes are worse when fever is present in the post-stroke patient populations.

Two studies reviewed utilized the mRS as their outcome measures for both ischemic stroke and intracerebral hemorrhage. The primary outcome measure from the Middleton et al. (2018) study was mRS greater than two at 90 days-post-stroke was considered functionally dependent. Greer et al. (2008) also discussed mRS and several other outcome measures, including mortality, LOS, Glasgow Outcome Scale, Barthel index, and Canadian Stroke Scale. Both Middleton et al. (2018) and Greer et al. (2008) found that mRS was significantly affected when fever is present in post-stroke patient populations. Middleton et al. (2018) found that patients who experience one febrile event within the first 72 hours of admission and patients with higher mean temps were associated with mRS greater than two. Although, Greer et al. (2008) found significance with mRS they did not establish what score is considered functionally dependent.

The National Institute of Health Stroke Scale (NIHSS) is an acute assessment scale of stroke severity. Rocco et al. (2007) utilized a change in NIHSS assessment at admission and discharge to a more severe class of stroke as its outcome of measure. Hyperthermia as a medical complication was associated with a shift to a more severe class of stroke. Rocco et al. (2007) also found that hyperthermia was associated with a higher risk of mortality. Medical complications associated with a change to a more severe class of stroke included urinary tract infections, hypertension, hyperglycemia, and hypoxia. Similar to Rocco et al. (2007), Kammergard et al. (2002) utilized mortality as an outcome measures. Mortality was measured at both three months and five years.

Long-term assessment of stroke patient outcomes that includes five years is not common with the research reviewed for this paper. Kammergard et al. (2002) measured admission body temperature in post-stroke patients and assessed how that correlated with mortality. Hyperthermia was associated with mortality rates at five years but not three months. Kammergard et al. (2002) discussed that for every one-degree drop in Celsius correlated with increased long-term survival. They also found diabetic patients clinically had more severe strokes than patients without diabetes.

Mortality rates are a common outcome measure found within the research articles listed in Appendix B. Saxena et al. (2015) assessed mortality rates in stroke patients related to peak temperature within the first twenty-four hours of admission. Higher peak temperatures were found to impact increased in-hospital mortality rates directly. It was also found that as the peak temperatures climbed the odds of mortality increased.

**Summary:** Hyperthermia displayed influence in all five studies that assessed both ischemic stroke and intracerebral hemorrhage patient populations. Greer et al. (2008) had the

highest level of evidence of the five studies utilized and the presence of fever was shown to have multiple impacts on stroke outcomes including mRS. Middleton et al. (2018) was the next highest level of evidence as prospective randomized controlled trial. Their results also displayed poor functional independence when fever is present with its elevated mRS. Finally, Rocco et al. (2007) did a prospective comparative study that found a change to a more severe class of stroke from admission to discharge in terms of NIHSS. Fever was also found to be associated with a higher risk of mortality.

Two retrospective comparative studies that included both ischemic stroke and intracerebral hemorrhage. Kammersgard et al. (2002) did a retrospective comparative study utilizing mortality as an outcome measure and found hyperthermia was significant at five years but not three months. It is also worth discussing that hyperthermia was found to be associated with a more severe class of strokes. Saxena et al.'s (2015) was also a retrospective comparative study. It was found that stroke patients were associated with higher mortality rates when peak temperatures were higher within the first twenty-four hours.

The presence of fever affects several different aspects of stroke assessment and outcome. Functionality dependence can be measured by mRS, which is shown to be influenced by hyperthermia. Stroke outcome scales including Barthel Index, and Glasgow Outcome Scale that display worse outcomes when fever is present. Mortality rates and stroke assessment scales, including the Canadian Stroke Scale, and the NIHSS, demonstrate higher scores when patients are hyperthermic. When fever is present in both ischemic stroke and intracerebral hemorrhage patient populations, there are worse patient outcomes than when fever is not present.

Temperature was defined differently in three of the five studies identified as including both ischemic stroke and intracerebral hemorrhage patient populations. Middleton et al. (2018)

and Saxena et al. (2015) defined hyperthermia as greater than 37.5 degrees Celsius.

Kammersgard et al. (2002) defined hyperthermia as greater than 37 degrees Celsius , and Rocco et al. (2007) defined hyperthermia as greater than 37.8 degrees Celsius. Greer et al. (2008) utilized multiple research studies in its analysis and temperature definition in terms of hyperthermia was not discussed.

### **Ischemic Stroke**

*Purpose:* A total of eight studies were reviewed (see Appendix B) that assessed patient outcomes in relation to fever and ischemic stroke. Two of the eight studies were meta-analyses and are the highest level of evidence referenced for ischemic stroke populations. Hajat et al. (2000) completed a meta-analysis that included nine studies with a total of 3,790 patients. Hajat et al. (2000) compared normothermic and hyperthermic ischemic stroke patient outcomes. Prasad et al. (2010) also completed a meta-analysis that included six studies with a total of 2,986 patients. In addition, Prasad et al. (2010) assessed the effect fever had on mortality within one month of suffering an ischemic stroke. Both of these studies are of a higher level of evidence and are an important consideration when applying the outcomes measured to ischemic stroke patient populations.

Six of the eight studies that assessed fever outcomes in ischemic stroke were prospective non-randomized or retrospective comparative studies. These studies had unique purposes in assessing the relation to fever and ischemic stroke patient outcomes. The aim of Geurts et al. (2016) was to assess ischemic stroke patients' temporal profile of body temperatures during the first three days of admission and apply it to functional outcome and cerebral infarction size. This study was unique because of its goals to assess cerebral infarction size and its correlation to hyperthermia. Leira et al. (2006), like Guerts et al., had several purposes, including the

assessment of cerebral infarction size with relation to fever. Leira et al. (2006) had additional purposes to assess serum pro-inflammatory makers and stroke severity related to hyperthermia. The assessment of pro-inflammatory markers is unique and not commonly measured with the stroke patient populations.

Endovascular thrombectomy is a therapy that is utilized in ischemic stroke patients. This procedure is performed in an interventional radiology setting involving emboli retrieval within large cerebral vessels. Powers et al. (2019) lists endovascular thrombectomy as a class one recommendation for treating ischemic stroke. The aim of Diprose et al. (2020) was to assess body temperature in the setting of endovascular thrombectomy. Their purpose was to identify patient outcomes when fever is present regarding pre- and post-endovascular thrombectomy. Powers et al. (2019) discussed endovascular thrombectomy as a class one recommendation and is the gold standard of care within comprehensive stroke centers. Therefore, identifying how body temperature affects patient outcomes in the setting for endovascular therapy will aid in improved plans of care for prescribers.

Mortality is a frequent unit of measure within the studies reviewed. Phipps et al. (2011), Seo et al. (2008), and Saini et al. (2009) all utilized mortality as one of their primary outcome measures. Phipps et al. (2011) examined the association between fever, ischemic stroke patients, and in-hospital mortality rates. Saini et al. (2009) assessed the effect body temperature had on stroke patient outcomes in relation to febrile time increments. Saini et al. (2009) assessed body temperatures at designated time increments and assessed which time periods displayed significance on stroke patient outcomes. Seo et al. (2008) studied the impact fever had on stroke patient outcomes with in-hospital mortality and ICU length of stay.

**Outcomes:** Mortality rates related to fever and stroke were a common outcome measure found within the studies that addressed ischemic stroke. Hajat et al. (2000) and Prasada et al. (2010) both utilized mortality as their outcome measure. Hajat et al. (2000) found that short-term mortality rates of three months or less were significantly associated with fever in the first twenty-four hours of admission. Hajat et al. (2000) also utilized morbidity as its outcome measure in post ischemic stroke patient populations. They found when fever is present within the first twenty-four hours of admission it was significantly associated with morbidity and worse patient outcomes. Prasada et al. (2010) discovered mortality rates are twice as likely when comparing afebrile and febrile patient populations in ischemic stroke.

Three of the ischemic stroke population studies that were retrospective and non-randomized prospective in nature also utilized mortality as their unit of outcome measure. Seo et al. (2008) compared outcomes between different temperature ranges; normothermia was  $< 36.7^{\circ}\text{C}$ , mild-thermia was  $37.6\text{-}38^{\circ}\text{C}$  and severe hyperthermia was classified as  $> 38^{\circ}\text{C}$ . Severe hyperthermia was found to have a ten time increase in-hospital mortality and an eight-time increase in ICU length of stay. Time to first hyperthermia and duration of hyperthermia was found to be non-significant. Mild hyperthermia was significant for increased length of stay but not mortality. Seo et al. (2008) also discussed that lower Glasgow Coma Scale, leukocytosis, and endotracheal tube placement all significantly increased the risk of in-hospital mortality

Similar to Seo et al. (2008), Phipps et al. (2011) utilized in-hospital mortality rates as their outcome measure. Phipps et al. (2011) assessed fever burden or the number of days with fever and compared in-hospital mortality rates. They found that medium and high fever burden were significantly associated with in-hospital mortality. Phipps et al. (2011) also identified that any fever in post-stroke populations was associated with a two-time increase with in-hospital

mortality rate. Phipps et al. (2011) noted that approximately 30% of stroke patients develop a fever. Diprose et al. (2020) utilized both functional independence and mortality at three months post-stroke as their outcome measure. They identified that higher median pre-endovascular temps were a significant predictor of both decreased functional dependence and three-month mortality. Diprose et al. (2020) also identified higher peak temperatures post endovascular therapy as a predicator of three-month mortality but not functional dependence.

Identifying when patients develop fever and how that correlates to outcome may aid prescribers in the plan of care development. For example, Saini et al. (2009) compared incremental time periods of fever development in post-stroke patient populations and applied that to 3-month mortality and functional outcome. Saini et al. (2009) identified fever at 8, 24, 48, 72 hours, and seven days was significant for poor long-term outcomes, yet fever at admission was not associated with 3-month mortality or poor functional outcome.

Two of the studies reviewed included ischemic stroke patient populations that assessed infarction volume in relation to fever. Guerts et al. (2016) primary outcome measure was infarction volume at three days and its relation to fever, while their secondary measure was fever and its relation to functional outcome. They found that fever was significantly related to increased infarction volume on days two, and three. Fever was also associated with poor functional outcome on day two and three. However, fever on admission was not significantly related to infarction volume or poor functional outcome.

Understanding how infarction volume correlates with fever and patient outcomes would offer greater insight into ischemic stroke patient outcomes. Leira et al. (2006) measured infarction volume in relation to fever. Their study found hyperthermia was related to higher infarction volume, higher stroke severity, and poor functional outcome. Leira et al. (2006) also

had several secondary measures and found hyperthermia was significantly related to hyperglycemia, and higher stroke severity at admission and three months. Blood levels for proinflammatory markers were also monitored and IL-6, TNF and ICAM-1 blood levels were found to be significantly elevated in the hyperthermia group.

**Summary:** Fever was reflective in all eight studies utilized for ischemic stroke patient populations. The two meta-analyses Hajat et al. (2000) and Prasad et al. (2010) identified fever in ischemic stroke patient populations as significantly related to mortality. Hajat et al. (2000) also found increased rates of morbidity with fever development in ischemic stroke populations in addition, morbidity was identified as an outcome measure in several other ischemic stroke studies identified in Appendix B. Diprose et al. (2020) conducted a non-randomized prospective study that identified both morbidity and mortality were affected when fever is present. Geurts et al. (2016) also used a prospective non-randomized cohort study that found functional outcomes directly influenced ischemic stroke hyperthermic patients. Guerts et al. (2016) also discovered that cerebral infarction volume shared a direction relation to an increase in body temperature. The larger the infarction volume, the higher the body temperature.

The third ischemic stroke study identified in Appendix B which measured functional outcome was also a non-randomized prospective study. Saini et al. (2009) found that functional outcome and mortality at three months are directly affected by fever in ischemic stroke patients. The retrospective comparative study by Seo et al. (2008) found that temperatures greater than 38C drastically increased in-hospital mortality and hospital length of stay. Phipps et al. (2011) also a retrospective comparative study, assessed in-hospital mortality in febrile ischemic stroke patient populations and found that medium and higher fever burden significantly increases in-hospital mortality rates. Leira et al. (2006) was a non-randomized prospective study that

measured stroke severity, infarction volume, and proinflammatory markers in febrile ischemic stroke patients. Hyperthermia was found to be related to all three measures.

Body temperature was identified differently between the ischemic stroke studies. Leira et al (2006) identified fever as greater than 37.5C, Saini et al. (2009) greater than 37.2C, and Phipps et al. (2011) greater than 37.8C. Several of the other studies identified hyperthermia in terms of temperature ranges. Seo et a. (2008) utilized a body temperature range; normothermia was less than 37.8C, mild hyperthermia 37.6-38C, and severe hyperthermia was > 38C. Guerts (2016), and Diprose (2020) utilized temperature ranges, and both studies identified temp > 37C as higher median temperatures. Understanding what is considered a fever in ischemic stroke patients is essential when developing proper treatment plans.

Functional outcome was measured by mRS in three of the ischemic stroke studies located in Appendix B. There was a small margin in what was considered a poor functional outcome. This poor functional outcome was identified as an mRS of either greater than two or three. Various measures for mortality with the ischemic stroke studies were also described. Mortality was either measured during inpatient or at three months. Stroke severity was measured by either the Canadian stroke scale or NIHSS. Canadian stroke scale greater than seven and NIHSS greater than sixteen were considered significant.

### **Intracerebral Hemorrhage**

**Purpose:** Patients who suffer from a hemorrhagic stroke can have long-standing morbidity issues and increased mortality rates. Patients who suffer from hemorrhagic stroke make up 13% of all strokes (CDC, 2020). These patient populations are at risk for many medical complications, including fever (Wartenberg et al., 2006). Understanding the effects of hyperthermia on hemorrhagic stroke can help optimize prescribers' plans of care in managing the

disease process. Rincon et al. (2012) described fever as a common occurrence with intracerebral hemorrhage (ICH). The purpose of the Rincon et al (2012) study was to assess body temperature related to hematoma growth and identify the presence of fever in ICH, finding an association between functional outcomes.

Identifying the difference between central fever development and infectious fever is the purpose of several of the hemorrhagic stroke studies reviewed. For example, Honig et al. (2015) assessed several components of fever in hemorrhagic stroke, striving to identify if central fever versus infectious fever is related to ICH and patient outcomes. In addition, the authors aimed to identify if hyperthermia development was significant with larger ICH strokes and in patient populations that developed intra-ventricular hemorrhages.

Hemorrhagic stroke can present with various etiologies including a ruptured aneurysm. Kramer et al. (2017) discussed cerebral aneurysmal rupture as commonly present in the form of aneurysmal subarachnoid hemorrhage. Kramer et al. (2017) discussed hyperthermia as a common occurrence with subarachnoid hemorrhages. Their study also discussed the likeness related to the development of vasospasm and the presence of blood in the ventricles. The purpose of the Kramer et al. (2017) study was to identify fever cause in subarachnoid hemorrhage patient populations and apply findings to patient outcomes. Their aim was to assess a temporal profile of fever development and apply findings to functional outcomes. Wartenberg et al. (2006) sought to determine the frequency of medical complications in subarachnoid hemorrhage patient populations. Their goal was to apply all medical complications and identify which complication significantly affects patient outcomes.

**Outcomes:** Functional outcome was a measure that all four ICH studies utilized. Honig et al. (2015) had several outcome measures including functional outcomes. The study measured

both mortality and functional outcome as ninety days. Honig et al. (2015) were also unique in the fact they separated infectious and central fevers. The majority of the studies listed in Appendix B only assessed fever development not infectious versus central. Honig et al. (2015) found that 32% of the ICH patient population developed central fevers. The study also found that larger ICH and intra-ventricular hemorrhages were associated with an increased risk of developing a central fever. Honig et al. (2015) also discussed both infectious and central fever were associated with decreased functional outcome and higher mortality rates. Patients that develop central fever have a 29% survival rate as compared to an 80% survival rate in patients that are afebrile. Also, when comparing central fever versus no fever, projected lifespan was significantly less in the central fever population.

Identifying the difference between infectious fever and central fever can change the prescriber's plan of care. Kramer et al. (2017), similar to Honig et al. (2015), included an outcome measure with identification of central versus infectious fever. Kramer et al. (2015) found that 56% of fever development in subarachnoid patient populations were central fevers. Kramer et al. (2015) also measured functional outcome at six and twelve months. The presence of fever and fever onset in less than twenty-four hours compared to no fever were found to have poor functional outcomes. Consecutive days with fever were the strongest predictor of poor functional outcome. It is also worth mentioning that a febrile temperature was recorded in 91% of the subarachnoid hemorrhage patient populations.

Subarachnoid hemorrhages are a unique form of ICH because blood can travel with limited restriction to different areas of the brain such as the ventricles and hypothalamus. Kramer et al. (2015) discussed medical complications as common with subarachnoid hemorrhage. They also discussed how medical complications exacerbate poor patient outcomes. Wartenberg et al.

(2006) had inclusion criteria solely for the patients with spontaneous or aneurysmal subarachnoid hemorrhage. Their study outcome measure was medical complications including fever and its effect on functional outcome at three months. Fever was identified as the most frequent medical complication and significantly effect on decreased functional outcomes. Fever development was found in 54% of the patient cohort.

Understanding fever when applying it to ICH hematoma growth may help provide greater insight into patient outcomes in hemorrhagic stroke. Rincon et al. (2012) established outcome measures of fever with relation to hematoma growth and ninety-day functional outcome. Their study also measured various clinical outcome measures related to ICH patients. Rincon et al. (2012) discussed fever as having significance with hematoma growth at twenty-four and seventy-two hours. However, hematoma growth was not related to fever at 48 and 168 hours. Poor functional outcome was also related to hematoma growth greater than 33%, hematoma volume greater than 15mL at admission, fever, intra-ventricular hemorrhage, diabetes, HTN, and age.

**Summary:** The four studies reviewed had inclusion criteria specific to ICH. These studies consisted of three retrospective and one non-randomized prospective study. Two of the studies had an inclusion criterion specific to subarachnoid hemorrhage. Kramer et al. (2015), and Wartenberg et al. (2006) completed retrospective comparative studies that exclusively measured patient outcomes in subarachnoid hemorrhage stroke populations. They both found that fever is a common medical complication, and that functional outcome is significantly affected with hyperthermia development.

The other two studies were more generalized to ICH patient populations. Rincoin et al. (2012), a retrospective study, found that fever is common in hematoma growth and significantly affects functional outcomes. Honig et al. (2015), a non-randomized prospective study found that

32% of fever development in ICH patient populations is a central fever. Rincoin et al. (2012), and Honig et al. (2015) found that larger ICH is associated with fever. Honig et al. (2015) also found that larger ICH with intra-ventricular hemorrhage was significantly associated with central fever. Fever displayed significant effects on both ninety-day morbidity and mortality outcomes.

Hyperthermia was defined differently within each of the ICH studies. Each of the studies reviewed for fever defined it uniquely. Honig et al. (2015) defined fever as greater than 38.5C, Kramer et al. (2017) as greater than 38.3C, Rincon et al. (2012) defined fever as greater than 37.5C, and Wartenberg et al. (2006) defined fever as greater than 38.3C. Functional outcome was also defined differently between the ICH studies. Wartenberg et al. (2006) and Rincon et al. (2012) defined poor functional outcome as mRS greater than three, whereas Kramer et al. (2017) and Honig et al. (2015) defined poor functional outcome as mRS greater than two. Defining what is considered significant in terms of fever and poor functional outcome is important when understanding ICH patient outcomes.

### **Fever Treatment Outcomes**

*Purpose:* Identifying the proper treatment plans for stroke patients when they develop fever is vital for improving patient outcomes. There are three main interventions for fever management in stroke patients. These include anti-pyretic medications, and both external and endovascular temperature management devices. Identifying which therapies are associated with improved stroke patient outcomes is the goal of this section. Fang et al. (2017) assessed the efficacy of fever management in both ischemic stroke and ICH patients to assess body temperature reduction and functional outcome with acetaminophen administration in febrile stroke patients. Identifying if acetaminophen therapy has significance to improved stroke patient outcomes is important in a prescriber plan of care development.

When incorporating external or endovascular cooling, identifying a targeted temperature is essential when selecting appropriate therapy. Kuczynski et al.'s (2020) purpose was to identify the clinical efficacy in hypothermia treatment of febrile ischemic stroke patients. Kuczynski et al. (2020) targeted temperature interventions included ice packs, surface, and endovascular cooling. It should also be noted that the median temperatures targeted when averaging all the studies was 33C. One limitation of their study was it did not utilize one temperature management intervention but multiple. The results of this study should be utilized for addressing the concept of therapeutic hypothermia and not for each intervention used to achieve targeted temperature.

Identifying evidence-based treatment plans for stroke patients that develop fever is important for improved patient outcomes. The purpose of Lakhan et al. (2012) was similar to Kuczynski et al. (2020) to assess the efficacy of therapeutic hypothermia in febrile stroke patients. Lakhan et al. (2012) aim was to identify if induced therapeutic hypothermia improves stroke patient outcomes when developing a fever. The interventions utilized were both external cooling and endovascular therapeutic hypothermia. This study also had a median targeted temperature range of 33C.

**Outcomes:** Fever management in stroke patients needs to be better understood. Powers et al. (2019) discussed hyperthermia as having a higher in-hospital mortality rate than normothermia. Unfortunately, the literature search performed could not identify studies exclusive to normothermia verse hyperthermia patient populations. Kuczynski et al. (2020) completed a systematic review and meta-analyses that utilized therapeutic hypothermia intervention and functional outcome as its outcome measure. Their aim was to measure functional outcome and medical complications in febrile stroke patients. Kuczynski et al. (2020) found that therapeutic hypothermia did not improve functional outcome in febrile stroke patients. However, the study

did identify that targeted therapy of external cooling device on the head showed benefit in functional outcomes. Kuczynski et al. (2020) also identified that cooling for greater than forty-eight hours compared to twenty-fours showed improved patient outcomes. Although, therapeutic hypothermia was not significant for improving patient outcomes; it did show a trend toward an improved functional outcome.

Therapeutic hypothermia treatment was identified in two separate studies reviewed. Lakhan et al. (2012) measured clinical outcome in febrile stroke patients who received targeted temperature therapy. Therapeutic hypothermia was shown to have no significant effect on improved stroke severity or functional outcome. Lakhan et al. (2012) discussed the need to explore targeted temperatures that compared normothermia intervention and hyperthermia. Their study also addressed a need for more large-scale randomized control trials that addressed therapeutic hypothermia outcomes.

Medication therapies were also discussed to lower body temperature and stroke patient outcomes. Fang et al. (2017) established outcome measures of temperature reduction with acetaminophen administration and functional outcome. The study found that significant temperature reduction was related to acetaminophen administration at twenty-four hours but not five days. Fang et al. (2017) also discussed the administration of acetaminophen to febrile stroke patients as having no functional improvement compared to the control group. Acetaminophen appeared to provide no functional improvement in febrile stroke patient outcomes.

**Summary:** The research studies utilized in assessing hyperthermia intervention in febrile stroke patients were all a very high level of evidence. Fang et al. (2017), Kuczynski et al. (2020), and Lakhan et al. (2012) were all systematic reviews and meta-analyses. A common theme among the three studies was that temperature control in hyperthermic stroke patients does not

improve patient outcomes. Fang et al. (2017) found fever reduction with acetaminophen was effective at twenty-four hours but not five days. Their study also revealed that acetaminophen treatment does not correlate with improved stroke patient outcomes.

Two studies utilized therapeutic hypothermia as their instrument to measure functional outcomes. These studies were not exclusive to a single modality but multiple modalities that included external cooling and endovascular targeted temperature therapy. Lakhan et al. (2012) showed no improvement of stroke severity or functional outcome in the therapeutic hypothermia cohort. Kuczynski et al. (2020) found that therapeutic hypothermia did not improve functional outcomes compared to the control group. However, this study did identify a trend of functional improvement with the hypothermia group, but not enough to show significance. Mortality rates were also similar when comparing hyperthermia to the therapeutic hypothermia cohort.

### **Clinical Guidelines Review**

Two clinical guidelines were also reviewed for this literature review (Ntaios et al. 2015, and Powers et al. 2019). See Appendices D and E to review these guidelines using the AGREE II appraisal. The Powers et al. (2019) guideline was for the managing acute ischemic stroke patient populations. This guideline is germane for the current topic, as Powers et al. (2019) discussed how sources of elevated temperature should be identified, and that treatment with acetaminophen should be utilized to reduce hyperthermia. Powers et al. (2019) identified the hyperthermia threshold as 38C. Induced hypothermia was found to have uncertain benefits. Their recommendations included a further need for a higher level of evidence pertaining to both induced hypothermia and normothermia.

Overall, the Powers et al. (2019) guideline is an excellent tool for managing arterial ischemic stroke. The guideline was updated from an earlier version with the most recent and

highest level of evidence available. A strength of the guideline was that research guided each intervention. Allowing for clear understanding as to the evidence behind each recommendation. They also created a ranking system to better understand the evidence quality to support each intervention. The guideline was also clear and easily transferrable into practice. The overall AGREE II score for the guideline is high and should be instituted into bedside practice for arterial ischemic stroke patient populations.

The guideline by Ntalos et al. (2015) also addresses temperature management in stroke patients, noting improved stroke patient outcomes are not related to hyperthermia management. These temperature management interventions include anti-pyretics, induced hypothermia, and normothermia therapies. Ntalos et al. (2015) also discussed the strengths of these recommendations as weak because of a limited amount of high-level evidence. These authors note the need for more randomized controlled trials regarding the treatment of fever in stroke patient populations.

Ntalos et al. (2015), and Powers et al. (2019) address the clinical questions proposed with their recommendations. The guideline established a clear link with evidence used to support the guideline recommendations. The quality of the guideline is high, with a detailed discussion of both the current body of knowledge regarding the guideline clinical questions and the recommendations suggested. The research utilized to help guide the recommendation was very transparent and allowed the reader to assess the quality of the recommendation.

### **Concept Map**

The concept map is located in Appendix C. Several consequences were identified from the evidence gathered for this inquiry. Fever development in stroke patients was found to significantly affect the outcome. Fever development consequences in stroke patients include

increased mortality, increased stroke severity, elevated pro-inflammatory markers, increased length of hospital stay, poor functional outcome, and increased hematoma and infarction volume with cerebral tissue. The treatment modalities were all found to reduce hyperthermia. There appears to be a straightforward consequence to fever development in stroke patients including worsening morbidity and increased mortality.

## **Conclusions, Implications, and Recommendations for Nursing**

### **Introduction**

The purpose of the inquiry was to determine stroke patient outcomes when fever is present. The results from this integrative review will help prescribers' better understand stroke patient outcomes when fever is present. This inquiry aimed to identify stroke patient outcomes in the acute care setting when fever is present. The findings from the literature may enhance prescribers' knowledge regarding stroke patient outcomes. It will also assist with building a common understanding between prescribers. Standardizing care and prioritizing fever with plans of care will help contribute to improved stroke patient outcomes when fever is present.

### **Conclusions**

The stroke patient populations chosen for this inquiry included ischemic and hemorrhage strokes. When a fever was present in both ischemic and hemorrhagic stroke patient populations, the evidence revealed there were poor patient outcomes. Five studies included both ischemic and hemorrhagic stroke patient populations. Functional outcome was measured by mRS in both Greer et al. (2008) and Middleton et al. (2018); these studies found when stroke patients become hyperthermic that result was higher mRS scores and poor functional outcome. Kammersgard et al. (2002), and Rocco et al. (2007) assessed stroke severity in febrile stroke patients and found stroke severity to be worse when hyperthermia was present. Mortality was also a common unit of

measure in both ischemic and hemorrhagic stroke patients. Several studies found when stroke patients develop fever, mortality rates were significantly higher in the febrile cohort (Kammersgard et al. 2002; Rocco et al. 2007; Saxena et al. 2015).

Eight studies reviewed for this inquiry were exclusive to ischemic stroke patient populations. Mortality was the most common unit of measure in febrile ischemic stroke patients and was found to be significantly associated with fever and ischemic stroke (Diprose et al. 2020; Hajat et al. 2000; Phipps et al. 2011; Prasad et al. 2010; Saini et al. 2009; Seo et al. 2008). Functional outcome was also measured in three of the studies. Several authors (Diprose et al. 2020; Geurts et al. 2016; Hajat et al. 2000; Saini et al. 2009) identified significantly worse functional outcomes in hyperthermic stroke patients. Larger areas of brain ischemia or infarction volumes were also found to be significantly related to the development of fever. (Guerts et al. 2016; Leira et al. 2006). Leira et al. (2006) found that stroke severity and pro-inflammatory markers were significantly elevated in hyperthermic ischemic stroke patients.

Intracerebral hemorrhage was exclusive to four of the studies with this inquiry. Functional outcome was found to be significantly worse in febrile hemorrhagic stroke patients (Kramer et al. 2015, Rincoin et al. 2012, & Wartenberg et al. 2006). Kramer et al. (2015), and Wartenberg et al. (2006) also discovered that ICH patients who develop a subarachnoid hemorrhage are the most likely to develop fever as a medical complication. Rincoin et al. (2012) identified fever to be significantly associated with ICH hematoma growth. Rincoin et al. (2012), and Honig et al. (2015) also identified larger ICH to be associated with fever. In addition, larger ICH have been identified as significantly associated with intra-ventricular hemorrhage which is also correlated with the development of central fever and worse patient outcomes (Honig et al. 2015).

Two guidelines were assessed regarding the treatment of fever in stroke patients (Ntalos et al. 2015; Powers et al. 2019). Powers' et al. (2019) guideline was exclusive to ischemic stroke patient populations and found that treating febrile stroke patients with acetaminophen was beneficial in reducing hyperthermia. The research also identified induced hypothermia as having uncertain benefits. Powers et al. (2019) identified 38C as the fever threshold. Ntalos et al. (2015) discussed hyperthermia treatment in febrile stroke patients, including acetaminophen, normothermia, and induce hypothermia was not significant for improved patient outcomes. Both guidelines addressed the need for a higher level of evidence with treatment interventions for febrile stroke patients.

This inquiry also assessed three systematic reviews and meta-analysis studies that measured stroke patient outcomes with the treatment of fever (Fang et al. 2017; Kuczynski et al. 2020; Lakhan et al. 2012). Therapeutic hypothermia as a treatment intervention for hyperthermia in stroke was found to have no significant benefit to stroke patient outcomes (Kuczynski et al. 2020; Lakhan et al. 2012). Acetaminophen was found to provide fever reduction in the first twenty-four hours but not at five days (Fang et al., 2017). However, when acetaminophen was administered for fever, stroke patient outcomes displayed no improvement.

### **Implications for Interdisciplinary Teams**

The interdisciplinary team generally includes Registered Nurses (RN), Advanced Practice Providers, Physicians, and ancillary staff. The following section discusses how the research findings from this inquiry apply to the interdisciplinary teams responsible for the plan of care development in stroke patients. The case study presented in the introduction of this inquiry highlighted the need for a common understanding of how fever affects stroke patient outcomes. It was discussed that there continues to be inconsistencies between prescriber' plan of care

development with stroke patients. The inconsistency is largely due to a lack of shared understanding with how fever affects stroke patient outcomes. The setting for this inquiry was acute inpatient care of stroke patients.

The research findings from this inquiry directly apply to how the interdisciplinary care team approaches fever in stroke patients. Fever development has been a common medical complication with stroke patients (Wartenberg et al., 2006). Fever is so common that guidelines have been developed with key recommendations for managing hyperthermia in stroke patients (Ntalos et al., 2015; Powers et al., 2019). The knowledge provided from this inquiry provides common understanding of how fever affects stroke patient outcomes. The implications from this inquiry provide a knowledge base for the interdisciplinary care team in managing care of febrile stroke patients properly.

## **Recommendations**

The following sections review the recommendations for research, education, and practice with stroke patients who develop a fever. These recommendations are based on the literature reviewed for this inquiry.

***Research Recommendations.*** The research recommendations from this inquiry found that stroke patient outcomes are worse when hyperthermia is present. Poor patient outcomes were found in ischemic and hemorrhagic strokes when hyperthermia is present. When stroke patients developed fever mortality rates were higher, functional outcome was worse, mRS > 2, increased stroke severity, elevated pro-inflammatory markers, increased hospital length of stay, larger infarction volumes, and larger hematoma volumes were present. This data is represented in a concept map located in Appendix C. When comparing different forms of ICH, subarachnoid and intra-ventricular hemorrhages were found with the highest presence of fever (Honig et al.,

2015). These two patient populations were also found to have the highest mortality rates. The research findings suggest that when fever is present, stroke patient outcomes are worse.

The threshold for what is considered febrile displayed slight variation between the ischemic and hemorrhagic stroke cohorts. In ischemic stroke patient populations, the fever threshold ranged from 37C-38.5C. The ICH research cohorts displayed a range of 37.5C-38.5C. The guideline recommendation from Powers et al. (2019) identified the fever threshold at 38C. Understanding what is considered febrile aids with further understanding for the interdisciplinary teams in identifying hyperthermia in stroke patients. Fever threshold is further discussed in the practice recommendations area of this inquiry. When attempting to treat hyperthermia in stroke patients; Ntalos et al. (2015) and Powers et al. (2019) discuss the need for a higher level of evidence in research. This need for a higher level of evidence suggests that further data on treatment modalities in febrile stroke patients to better understand outcomes.

***Education Recommendations.*** Shared understanding between interdisciplinary teams must be found with stroke patients when fever is present. The next steps would be for any healthcare system to provide continuing education regarding the recommendations provided from this inquiry. This education should include the higher levels of mortality and morbidity that is found in stroke patients who develop a fever. This education intervention needs to be done throughout the interdisciplinary team. The nursing education piece can be dedicated to the clinical nurse specialists (CNS) and nurse educator groups. Depending on the facility, the CNS group may also provide evidence-based practice recommendations to the APRN groups. The medical directors who oversee stroke care would also be a good resource for the physicians. The medical directors would be able to disseminate the findings from the inquiry to all the prescribers involved with stroke care management. The practice recommendations from this inquiry would

be a good reference for an education source. Getting the research and practice recommendations to the proper education channels is required for any successful practice change.

***Practice Recommendations.*** The practice recommendations vary depending on the therapy goals. The administration of acetaminophen has shown benefit in lowering patient temperatures but not improving patient outcomes. Evidence shows utilizing therapeutic hypothermia for temperature management in febrile stroke patients is non-significant with improving patient outcomes. Therapeutic hypothermia intervention has also been shown to be low risk with adverse events in stroke patient outcomes. Therapeutic hypothermia may be warranted if a hyperthermic stroke patient is facing a high degree of mortality. When targeting a temperature of normothermia, limited research was identified. Given that SAH and Ntalos et al. (2015), and Lakhan et al. (2012) discussed the need for higher levels of evidence in research with targeting normothermia temperature in stroke patients. Kuczynski et al. (2020), and Lakhan et al. (2012) also note further research is needed with stroke patients and normothermia therapy.

Patients who suffer subarachnoid hemorrhages with high stroke severity and large ICH with intra-ventricular extension have shown to have markedly worse patient outcomes (Honig et al., 2015; Wartenberg et al. 2006). There may be some benefit in these specific patient populations with targeted temperature management. Therapeutic hypothermia did show non-significant trends toward improved febrile stroke patient outcomes (Kuczynski et al., 2020, & Lakhan et al., 2012). This trend may be rationale enough to provide targeted temperature therapy in stroke patients with a high probability of mortality or poor functional outcome.

Understanding the threshold of what is considered hyperthermia and the ideology of fever development are also essential to practice recommendations. Depending on the patient population, the fever threshold can range from 37C-38.5C according to the research identified in

Appendix C. Utilizing a range of temperatures may make fever identification may give way to confusion. This is why fever should be identified with a temperature of 37.5 or greater. The source of fever must also be included in the prescribers' plans of care. Honig et al. (2015), and Kramer et al. (2015) discussed the importance of identifying central versus infectious fever in stroke patients. Infectious fever requires increased treatment modalities compared to central fever in stroke patients, such as antibiotic therapy. Ensuring appropriate care is developed when infectious fever is present was associated with significant improvement in stroke patient outcomes.

### **Summary**

Fever is a common medical complication in stroke patient populations. Stroke patient outcomes are significantly worse when fever is present. Identifying a proper treatment course for febrile stroke patients can be complex. The interdisciplinary team must consider each stroke patient's clinical picture when developing a proper treatment plan of care. The evidence presented in this inquiry provides a base for the plan of care development. Identifying the source of infection has shown benefits to improved patient outcomes. Targeted temperature management may be indicated in subarachnoid hemorrhages, large ICH, and intra-ventricular hemorrhages. When fever develops in stroke patients, the interventions utilized to manage hyperthermia appear to have mixed outcomes. The findings in this inquiry also suggest a need for further inquiry regarding targeted temperature management and stroke patient outcomes. However, one thing is clear from the evidence reviewed; when fever is present stroke patient outcomes are worse.

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## Appendix A

## Literature Search Dates, Keywords, Sources, and Results

| Date of Search | Keyword Used                                                                                              | Database/Source Used<br>(CINAHL, OVID,<br>Proquest, Google<br>Scholar, etc.) | # of Hits |          |      |
|----------------|-----------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------|-----------|----------|------|
|                |                                                                                                           |                                                                              | Listed    | Reviewed | Used |
| 09/20/2020     | Stroke or cerebral vascular accident or CVA, fever or febrile or temperature or pyrexia, patient outcomes | CINAHL                                                                       | 367       | 15       | 3    |
| 9/26/2020      | Stroke or cerebral vascular accident or CVA, fever or febrile or temperature or pyrexia, patient outcomes | CINAHL                                                                       | 366       | 10       | 3    |
| 9/28/2020      | Stroke or cerebral vascular accident or CVA, fever or febrile or temperature or pyrexia, patient outcomes | CINAHL                                                                       | 367       | 15       | 2    |
| 1/10/2021      | Stroke or fever or patient outcomes                                                                       | PubMed                                                                       | 472       | 15       | 4    |
| 1/20/2021      | Stroke or fever or patient outcomes                                                                       | PubMed                                                                       | 470       | 20       | 4    |
| 3/28/2021      | Stroke or fever                                                                                           | Cochrane                                                                     | 226       | 15       | 5    |

## Appendix B

## Stroke Patient Outcome when Fever is Present Literature Review

| Citation                                                                                                                                                                             | Purpose                                                                                                                                                                                                                                  | Sample/<br>Setting                                                                                                                                                                                                                                   | Design/<br>Framework                          | Variables/<br>Instruments                                                                                                                                                                                                                                                                                                                                                                                                                         | Results                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Implications                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Comments                                                                                                                                                                                                                                                                                                                                                       | Level of<br>Evidence |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------|
| Bush, R., et al. (2018). Fever burden and health-related quality of life after intracerebral hemorrhage. <i>Neuro critical care</i> . 29(2), 189-194. doi: 10.1007/s12028-018-0523-y | <p>-“We sought to examine the independent effect of fever on health-related quality of life in ICH pts” (p. 190).</p> <p>-“Few data specifically examine the issue of fever and health-related quality of life in ICH pts” (p. 189).</p> | <p>-ICU referral setting for stroke.</p> <p>-N=109</p> <p>-Sample data collected from 2011-2015</p> <p>-Exclusion criteria ICH r/t trauma, hemorrhagic conversion of ischemic stroke, and structural lesion including arteriovenous malformation</p> | -Prospective non-randomized comparative study | <p>-Fever burden was defined as the number of days w/ a temp &gt;100.4F</p> <p>-NIHSS was assessed during hospital admission</p> <p>-Health-related quality of life was measured at 28 days, 3 months, and 1 year</p> <p>-mRS was assessed at 28 days, 3 months, and 1 year.</p> <p>-Extended list of clinical risk factors that may relate to study outcomes</p> <p>-Significant data <math>p&lt;0.05</math> &amp; T-score changes of 0.5 SD</p> | <p>-mRS at 28 days, 3 months, &amp; 1 year were significant w/ relation to fever (<math>p&lt;0.05</math>)</p> <p>-Each additional day of fever was predictive of a lower mobility T-score -0.9 &amp; cognitive function T-score -1.3.</p> <p>-Mobility scores at 28 days (<math>p&lt;0.0001</math>), 3 months (<math>p&lt;0.004</math>), and 1 year (<math>p&gt;0.2</math>),</p> <p>-Cognitive function at 28 days, 3 months, and 1 year (<math>p&lt;0.05</math>).</p> | <p>-Fever burden was an independent predictor of worse cognitive and mobility function in relation to health-related quality of life scores.</p> <p>-Temp &gt; 100.4 was treated w/ Tylenol, ice packs, and cooling blankets; study measures still displayed statistical significance.</p> <p>-Incidence of fever 39.6%.</p> <p>-Average ICH score was mild (1) which is reflective of pts that survive stroke event</p> <p>-Limitations: Data was from referral center which may not reflect other institutions. Did not discuss rationale for 1-year mobility score.</p> | <p>-Health-related quality of life is a more pts-centered measure of outcome compared to functional status.</p> <p>Function status typically measures ability to walk whereas health-related quality of life that captures cognitive status (balancing finances, managing tasks, &amp; following instructions w/ medications) and ability to manage ADL's.</p> | IV                   |

| Citation                                                                                                                                                                                                 | Purpose                                                                                                                                                                                                                                                                                                                       | Sample/ Setting                                                                                                                                                                                          | Design/ Framework                             | Variables/ Instruments                                                                                                                                                                                                                                                                                                                                                                                               | Results                                                                                                                                                                                                                                                                                                                                                                                              | Implications                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Comments                                                                                                                                                                                                                                                                                                                                                       | Level of Evidence |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|
| Diprose, W., et al. (2020). Impact of body temperature before and after endovascular thrombectomy for large vessel occlusion stroke. <i>Stroke</i> . 51(4), 1218-1225. doi:10.1161/STROKEA.HA.119.028160 | -“The impact of body temperature has not been well studied in the era of recanalization” (p. 1219).<br><br>-“We explored the relationship between clinical outcomes and per- and post-endovascular body temp, which serve as surrogates for the intra-ischemic and post-ischemic phases of large vessel occlusion” (p. 1220). | -Single-center tertiary hospital that provides endovascular therapy.<br><br>-Study period 2011-2019<br><br>-N=432<br><br>-Inclusion criteria: large vessel occlusion that required endovascular therapy. | -Prospective non-randomized comparative study | -Primary measure functional independence at 3 months.<br><br>-Secondary measures included an ordinal shift of mRS scores at 3 months, symptomatic ICH, and mortality at 3 months.<br><br>-mRS > 2 is functional dependence.<br><br>-Quartile temp range first 34.1-35.7C, second 35.8-36.1C, third 36.2-36.5C, & fourth 36.6-38.5C.<br><br>-Extended list of clinical risk factors that may relate to study outcomes | -Higher median pre endovascular temp significant predictor of mRS >2 & increased mortality at 3 months ( $p<0.05$ ).<br><br>-Higher peak temp post endovascular therapy was a significant predictor of mortality, higher mRS score ( $p<0.05$ ) but not functional independence ( $p>0.05$ )<br><br>-No significant outcomes w/ peak pre temps & median post endovascular intervention ( $p>0.05$ ). | -Every 1C increase in median body temp pre-endovascular there was a 34% lower odd of functional independence, 42% higher odds of poorer mRS score and 65%<br><br>-Higher peak post endovascular therapy body temp associated with adverse clinical outcomes.<br><br>-Limitations: No data displayed for percentage of sample size for quartile temp range. Single temp assessments were performed with pre-treatment populations which may have resulted in missed peak temp measurements. | -56% achieved functional independence, & 16% mortality rate at 3 months.<br><br>-Median NIHSS was 17 at admission<br><br>-83% anterior circulation & 17% posterior circulation large vessel occlusion.<br><br>-53% received alteplase, & 88% achieved successful recannulation.<br><br>-50% were treated with Tylenol for fever & 10% diagnosis with infection | IV                |

| Citation                                                                                                                                                                                                               | Purpose                                                                                                                             | Sample/ Setting                                                                                                                                                                                                                                                                                                                      | Design/ Framework                                                                                                                        | Variables/ Instruments                                                                                                                                                                                                                                                                              | Results                                                                                                                                                                                                                                                                                                                                                          | Implications                                                                                                                                                                                                                                                                                                                                                                                                             | Comments                                                                                                                                                                                                                                                                                              | Level of Evidence |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|
| Fang, J., et. al (2017). Effect of paracetamol (acetaminophen) on body temperature in acute stroke: a meta-analysis. <i>American Journal of Emergency Medicine.</i> 35(10), 1530-1535. doi: 10.1016/j.ajem.2017.03.039 | -“investigate the efficacy of acetaminophen in patients with acute stroke through a systematic review and meta-analysis” (p. 1531). | -Search of “Medline, SCOPUS, Google Scholar, EMBASE, Springer, and Science Direct” (p. 1532)<br><br>-Keyword search included “paracetamol/acetaminophen, AIS/ICH without limitation of language” (p. 1532)<br><br>-Participants: “patients with AIS or ICH and body temp > 36C” (p. 1531).<br><br>-N=5 studies, n=1,582 pts included | -Meta-analysis<br><br>-“Studies selected for analysis were either randomized controlled trials or controlled clinical trials” (p. 1531). | -Primary outcomes: body temp reduction at 24 hrs and 5 days.<br><br>-Secondary outcomes: functional outcomes in relation to mRS and adverse event.<br><br>-Measure: mRS < 2, fever defined as > 36C<br><br>-Variables: anti-pyretic medications as experimental group and placebo was control group | -Functional outcome with acetaminophen use was not associated with improved outcomes; RR of having mRS < 2 was 1.08 with no statistical significance (p=0.45)<br><br>-statistical significance of temp reduction at 24 hrs with acetaminophen (p=0.007)<br><br>-No statistical significance was shown with temp reduction at 5 days with acetaminophen (p=0.73). | -Acetaminophen administration when fever is present showed no benefit when compared to placebo drug on functional outcome.<br><br>-Acetaminophen does show to decrease temp in AIS and ICH patient populations at 24 hours but not at five days.<br><br>Limitations: No limitations section listed; four of the five studies were conducted > 15 years ago. 4 of the studies had very small sample sizes with their pts. | -Data may be outdated because several of the articles utilized were from 2003 or earlier.<br><br>-High-level of evidence because data was pulled from randomized controlled trials and controlled clinical trials<br><br>-The research does not directly address the clinical purpose of this inquiry | I                 |

| Citation                                                                                                                                                                                   | Purpose                                                                                                                                                                                      | Sample/<br>Setting                                                                                                                                                                                                                                                                                                                  | Design/<br>Framework                     | Variables/<br>Instruments                                                                                                                                                                                                                                                                  | Results                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Implications                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Comments                                                                                                                                                                                                                                                                                                                                                                                | Level of<br>Evidence |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------|
| Geurts, M., et al. (2016). Temporal profile of body temperature in acute ischemic stroke: relation to infarct size and outcome. BMC neurology. 16, 233-239. doi: 10.1186/s12883-016-0760-7 | -“In this study, we assessed temporal profile of the relation between body temperatures during the first three days after ischemic stroke and infarct size and functional outcome” (p. 234). | -14 different Dutch Acute Stroke Study Centers were included<br><br>-Data collection period May 2009-August 2013<br><br>-Inclusion criteria: AIS with symptom duration < 9 hrs, NIHSS > 1 or < 1 if thrombolytics given.<br><br>-Exclusion criteria: ICH & unknown symptom onset if > 9 hrs.<br><br>-AIS sample population 419 pts. | -Prospective non-randomized cohort study | -“primary outcome infarct volume at 3 days” (p. 234).<br><br>-Relation between temp and infarct size assessed by linear regression.<br><br>-Functional outcome was measured with mRS at three months; poor outcomes were > 2.<br><br>-AIS infarct size was measured on day 3 of admission. | -Adjusted linear regression analyses for each additional 1.0C increase in peak body temp on day one was associated with 0.31 ml (95% CI,0.04-0.59) increased infarct size, on day two with 1.13 ml (95% CI,0.83-1.43), and on day three 0.80 ml (95% CI,0.48-1.12) larger infarct size ( $p<0.05$ ).<br><br>-Every additional increase in 1.0C in peak body temp on day two and three the risk of poor outcome was 52% (95% CI,17-99%) and 47% (95% CI,22-77%). | -Average mean body temps were not associated with infarct size or poor functional outcome ( $p>0.05$ ).<br><br>-Admission body temp had no correlation to infarct size or functional outcome.<br>-Peak body temps and not mean body temps showed significance with infarct size and functional outcome.<br>.<br>-Limitations: No set method for temp assessment (rectal, tympanic, or oral); anti-pyretic treatment and infection rate was not accounted in data; infection rates. Confidence wide for increase in body temp on day two and three suggesting the need for bigger sample size. | -The average daily temp on day one was 37.3C, day two 37.3C, and day three 37.1C. The mean average temps are very low and below threshold of 37.5C which is commonly identified as the point of fever. The average temp recordings were all below 37.5C which may be rationale for non-significance in average mean temp.<br><br>-Treatment of fever up to three days has shown benefit | IV                   |

| Citation                                                                                                                                                                                        | Purpose                                                                                                                                                                                                                                  | Sample/<br>Setting                                                                                       | Design/<br>Framework              | Variables/<br>Instruments                                                                                                                                             | Results                                                                                                                                                                                                                                                                                                                | Implications                                                                                                                                                                                                                                                                                                                                                                                   | Comments                                                                                             | Level of<br>Evidence |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|-----------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|----------------------|
| Greer, D., et al. (2008). Impact of fever on outcome in patients with stroke and neurologic injury: a comprehensive meta-analysis. Stroke. 39(11), 3029-3035. doi: 10.1161/STROKEAHA.108.521583 | -“Assess the significance of the relationship between fever and outcome across the full range of neurological injury, including stroke, and its magnitude in distinct measures of clinical, functional, and economic outcome” (p. 3029). | -Search of MEDLINE databases from 1995-2006.<br><br>-39 studies utilized<br><br>-Pts sample size 14,431. | Systematic review & meta-analysis | -7 outcomes measured: mortality, Glasgow Outcome Scale, functional outcome, Barthel index, mRS, Canadian stroke scale, ICU length of stay, & hospital length of stay. | -Mortality (RR 1.5, effect size 0.46), Glasgow Outcome Scale (RR1.3, effect size 0.26), Barthel index (RR 1.9, effect size 0.65), mRS (RR 2.2, effect size 0.89), Canadian stroke scale (RR1.4, effect size 0.35), ICU length of stay (RR2.8, effect size 1.66), & hospital length of stay (RR 3.2, effect size 1.53). | -In all 7 outcomes measured significant association was found with pts that develop fever.<br><br>-The effect size for each outcome ranged from moderate Glasgow outcome scale (0.26) to large ICU length of stay (1.66).<br><br>-Limitations: Selection bias with only utilizing MEDLINE databases, 17 of the 39 studies were not prospective, & studies used different definitions of fever. | This study included traumatic brain injury pts populations which does not fit this clinical inquiry. | I                    |

| Citation                                                                                                                                                                        | Purpose                                                                                                                                                                                                                                                                 | Sample/<br>Setting                                                                                                                                                                                                               | Design/<br>Framework                                                                                                                                                      | Variables/<br>Instruments                                                                     | Results                                                                                                                                                                                                                                                                                                                     | Implications                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Comments                                                                                                                                                                                                                                                                                                               | Level of<br>Evidence |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------|
| Hajat, C., et al. (2000). Effects of poststroke pyrexia on stroke outcomes: a meta-analysis of studies in patients. <i>Stroke</i> . 31(2), 410-411. doi: 10.1161/01.str31.2.410 | <p>-“Undertake a meta-analysis on all published studies to investigate the effect of body temperature on stroke outcome” (p. 410)</p> <p>-“There are no large-scale prospective studies assessing outcome between normothermic and hyperthermic patients” (p. 410).</p> | <p>-Search of MEDLINE, BIDS and the Cochrane Library; studies included spanned 20-year period.</p> <p>-Prospective studies assessing outcome between normothermia and hyperthermia</p> <p>-N=9 studies utilized, n=3,790 pts</p> | <p>-Meta-analysis</p> <p>-searching “for all published studies that investigated the effect of body temperature after the onset of stroke on stroke outcome” (p.410).</p> | <p>-Variables: normothermia vs. hyperthermia</p> <p>-Instruments: morbidity and mortality</p> | <p>-Combined probability value for morbidity (<math>p&lt;0.0001</math>)</p> <p>-Combined probability value for mortality (<math>p&lt;0.00000001</math>)</p> <p>- The results “suggest a detrimental effect of hyperthermia on stroke outcomes, with some evidence of greater effect with early onset pyrexia” (p. 413).</p> | <p>-The results of the meta-analysis suggest that fever has a significant effect on stroke outcome. Patient outcomes were also shown to be affected to a greater extent when fever is present within the first 24 hours.</p> <p>-Limitations: Differences found between inclusion criteria and the type of stroke were varied between the individual studies. Inconsistency with temp measure and the definition of pyrexia <math>&gt;37.5</math> and <math>&gt;38.5</math> between the individual studies. The meta-analysis lacked discussion or flow diagram of study selection process. Study was conducted in 2000</p> | <p>The study was conducted in 2000. Utilizing this research in practice should be followed up with more recent data. Selection of this study for utilization with this inquiry is related to the higher level of evidence and how close the purpose of this study resembled the clinical question to this inquiry.</p> | I                    |

| Citation                                                                                                                                                                                           | Purpose                                                                                                                                                                                                                   | Sample/<br>Setting                                                                                                                                                                                                                                                                               | Design/<br>Framework                     | Variables/<br>Instruments                                                                                                                                                                                                                                                                                                                     | Results                                                                                                                                                                                                                                                                                                                                                                                                                                          | Implications                                                                                                                                                                                                                                                                                                                                                                                                            | Comments                                                                                                                                                                                                                                                                                                                                                                                                                                           | Level of<br>Evidence |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------|
| Honig, A., et al. (2015). Central fever in patients with spontaneous intracerebral hemorrhage: predicting factors and impact on outcome. BMC neurology. 15(6), 1-8. doi: 10.1186/s12883-015-0258-8 | -“to examine whether central fever is associated with spontaneous ICH, whether factors predicting the development of central fever can be identified and whether central fever influences outcome on pts with ICH” (p. 2) | -Hadassah Medical Organization; patients within this stroke registry presenting with spontaneous ICH; admitted from 2009-2010<br><br>-N=95<br><br>-Inclusion criteria: spontaneous ICH<br><br>-“every case of ICH that resulted from an etiology other than spontaneous ICH was excluded” (p. 2) | -Prospective non-randomized cohort study | -Measures included mortality rates and 90-day outcomes in relation to mRS.<br><br>-mRS favorable outcome was < 2.<br><br>-Central fever temp > 38.3C with no evidence of infection.<br><br>-Infectious fever temp > 38.3C with evidence of infection.<br><br>-No fever temp < 38.3C.<br><br>-Temps were taken within first week of admission. | -Mortality rates with central fever when compared to no fever were significant (80%, 29.1%, $p<0.001$ ).<br><br>-Mean peak temp for survivors 38.5C and 39C for deceased ( $p=0.035$ ).<br><br>-Peak temp was higher when fever started earlier ( $p=0.009$ ).<br><br>-Peak temp was significantly higher with central fever ( $p=0.003$ ).<br><br>-larger ICH and intra-ventricular hemorrhage were associated with central fever ( $p<0.001$ ) | -32% of pts that have ICH suffer from non-infectious central fever.<br><br>-Chi-square analysis revealed central fever associated with 100% unfavorable outcomes when compared to no fever 46.9% ( $p<0.001$ ).<br><br>-Mean projected lifespan for central fever and no fever (315, 1100 days, $p<0.001$ ).<br><br>-Limitations: Infectious fever sample size small ( $n=9$ ), non-randomized can lead to bias effect. | -Hematoma location and sub-arachnoid hemorrhage without intra-ventricular hemorrhage was not associated with central fever.<br>-Only sub-arachnoid hemorrhage with intra-ventricular hemorrhage was associated with central fever.<br>-No significant difference in mortality was found between central and infectious fever.<br>However, significance was found in 90-day outcome with central fever and infectious fever with mRS ( $p<0.001$ ). | IV                   |

| Citation                                                                                                                                                                      | Purpose                                                                                                                                                                                                                                                              | Sample/<br>Setting                                                                                                                                                                                                                                                   | Design/<br>Framework            | Variables/<br>Instruments                                                                                                                                                                                                                                                                                                                                                                       | Results                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Implications                                                                                                                                                                                                                                                                                                                                                                                                            | Comments                                                                                                                                                                                                                                                                                                                 | Level of<br>Evidence |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------|
| Kammersgaard, L., et al. (2002). Admission body temperature predicts long-term mortality after acute stroke. Stroke. 33(7), 1759-1762. doi: 10.1161/01.str.0000019910.90280f1 | <p>-“Evaluate whether body temperature on admission is an independent predictor of long-term prognosis after stroke” (p. 1759).</p> <p>-“Determine relation between admission body temp and long-term mortality in all patients admitted with stroke” (p. 1760.)</p> | <p>-Stroke unit at Bispebjerg Hospital, Denmark; 25-month study period.</p> <p>-Pts admitted within 6 hrs onset of stroke.</p> <p>-N=390 pts</p> <p>-Inclusion: ICH &amp; AIS</p> <p>-Exclusion criteria: transient ischemic attack or sub-arachnoid hemorrhage.</p> | Retrospective comparative study | <p>-Admission body temp and how that correlated with mortality rates at 3-months and 5 years.</p> <p>-Hyperthermia temp &gt; 37C and hypothermia temp &lt; 37C.</p> <p>-Scandinavian stroke scale utilized to assess stroke severity recorded at admission, weekly during hospital stay, and at discharge</p> <p>-Extended list of clinical risk factors that may relate to study outcomes.</p> | <p>Clinical characteristics of significance found in pts hyperthermia at admission were initial stroke severity, diabetes, 3 month &amp; 5 year survival rates (<math>p&lt;0.05</math>).</p> <p>-Hyperthermia vs. hypothermia at admission had increased stroke severity (30.2 vs 36.5) <math>p=0.001</math>.</p> <p>-Mortality rate at five years with hyperthermia compared to hypothermia 73 per 100 vs 59 per 100 (<math>p=0.001</math>).</p> <p>-3-month mortality rate non-significant in hyperthermia group (<math>p=0.5</math>)</p> <p>-every drop of 1C was an independent predictor of long-term mortality (HR 1.3, 95%CI 1.04-1.63).</p> <p>-Hyperthermia compared to hypothermia 1-year mortality rate (RR 3.4).</p> | <p>-Stroke severity was found to be significant with the hyperthermia group.</p> <p>-Every 1C drop in temp corresponded to a 30% difference in relative risk of long-term mortality</p> <p>-Hyperthermia shows correlation with long-term mortality rates at 1 and 5 years.</p> <p>-Hyperthermia shows no correlation to mortality at 3-months.</p> <p>-Limitations: No limitations section listed in this article.</p> | <p>-The study was conducted in 2001 but was utilized because it closely resembled clinical question and displayed to long-term results mortality results at 5 years.</p> <p>-Hyperthermia present in 54% of patients.</p> <p>-Did not elaborate on why mortality rates were different from 3-month to 1 and 5 years.</p> | IV                   |

| Citation                                                                                                                                                                                             | Purpose                                                                                                                                                                                                                             | Sample/<br>Setting                                                                                                                                                                                                                           | Design/<br>Framework      | Variables/<br>Instruments                                                                                                                                                                                                                                                                                                                                                                   | Results                                                                                                                                                                                                                                                                                                                                                                                       | Implications                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Comments                                                                                                                                                                                                                                                                                                                                                                                      | Level of<br>Evidence |
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| Kramer, C., et al. (2017). Refining the association of fever with functional outcome in aneurysmal subarachnoid hemorrhage. <i>Neurocritical Care</i> . 26(1), 41-47. doi: 10.1107/s12028-016-0281-7 | -“We pursued this study to evaluate the effect of febrile and subfebrile temp elevation due to infectious and noninfectious causes on clinical outcome in a large cohort of patients w/ aneurysmal subarachnoid hemorrhage” (p. 42) | -Multi-center study St. Mary’s, hospital & Rochester Mayo Medical Center; neurologic intensive care unit; between 2001-2013<br><br>-N=584<br><br>-Inclusion: Only aneurysmal subarachnoid hemorrhage patients diagnosed cerebral angiography | Retrospective comparative | -Outcome measures: Functional outcome assessed at 6 & 12 months; mRS < 3 considered functionally dependent; mRS >2 considered poor functional outcome<br><br>-Fever defined as > 38.3C on at least one measurement for two consecutive days.<br><br>-Febrile load defined as number of hours with temp > 38.3C<br><br>-Subfebrile temp 37-38.2C<br><br>-Clinical risk factors also assessed | -Presence of fever 48% w/ poor outcome 62% OR 2.3(95% CI1.6-3.3) & p<0.001<br><br>-Fever onset < 24 hrs 12% w/ poor outcome 19% OR 2.4(95% CI1.4-3) & p=0.001<br><br>-Fever onset < 72 hrs 19% OR 2.0(95% CI1.4-3.2) & p=0.0002<br><br>-Febrile load > 34 hours considered significant p<0.001<br><br>-Infectious fever and subfebrile patient populations considered non-significant p>0.05. | -The presence of fever < 24hrs, & < 72 hrs within two consecutive days considered significant for poor outcome.<br><br>-Temp < 38.3 considered not related to poor outcomes.<br><br>-Infectious fever although present in almost half of the febrile patient population it was not considered significant when applied to poor outcome.<br><br>Limitations: All fevers were treated with strict normothermia protocols and antibiotics given to infectious cohort which may have masked fever presence and not provided accurate clinical outcomes. | -One temp > 38.3C occurred in 91% of patient cohort<br><br>-Infectious fever occurred in 44% of the febrile patients.<br><br>-Days of fever considered strongest model of poor outcome.<br><br>-Clinical risk factors associated with poor outcome age > 55, active smoking, BMI > 30, modified fisher scale >3.5, ICH, IVH, blood transfusion (hemoglobin < 8.0), & cerebral edema (p<0.05). | IV                   |

| Citation                                                                                                                                                                                               | Purpose                                                                                                                                                                   | Sample/<br>Setting                                                                                                                                                                                                                                       | Design/<br>Framework               | Variables/<br>Instruments                                                                                                                                                                                                                                                                      | Results                                                                                                                                                                                                                                                                                                                                                                                                                                       | Implications                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Comments                                                                                                                                                                                                                                                                                                                                                                                                             | Level of<br>Evidence |
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| Kuczynski, A. (2020). Therapeutic hypothermia in acute ischemic stroke-a systematic review and meta-analysis. Current Neurology and Neuroscience Reports. 20(5), 1-10. doi: 10.1007/s11910-020-01029-3 | -“We aim to search and analyze the existing literature on the clinical efficacy and complications of inducing hypothermia in the acute phase of ischemic stroke” (p. 13). | -Search of MEDLINE databases<br><br>-Studies selected from 2000-2019 including controlled prospective and retrospective studies<br><br>-Sample size 12 prospective studies (8 RCT, & 4 prospective observational cohorts).<br><br>-Total of 779 patients | -Systematic review & meta-analysis | -Primary outcome was good functional outcome (mRS<2) at follow up.<br><br>-Secondary outcomes total complications including ICH, cerebral edema, pneumonia, cardiac complications, DVT, and mortality.<br><br>-Therapeutic hypothermia targeted temp was 33C except for two studies (32C-35C). | -Functional outcome did not differ (RR1.17, 95%CI0.93-1.46) at follow up.<br><br>-Cooling >48hrs showed greater overall improvement ( $p<0.05$ ).<br><br>-5 studies reported mRS shift towards improvement w/ therapeutic hypothermia ( $p=0.05$ ).<br><br>-Targeted hypothermia therapies vs systemic cooling showed improved functional outcome ( $p=0.01$ ).<br><br>-Overall, complications significant in hypothermia group ( $p<0.01$ ). | -All complications except for cardiac were comparable between groups.<br>-Only two studies assessed infarction volume; one reported less growth in hypothermia group and the other study reported smaller final infarction volume in hypothermia group.<br>-Improved function outcome was noted in all 4 prospective studies but not in the 8 randomized control studies.<br>-Shifts toward improved functional outcome was noted in the hypothermia group.<br>-Mortality was similar between the two groups.<br><br>-Limitations: one database utilized this may have lead to missed opportunity in identifying more data for review. | -Cooling variables highly variable between studies ice packs, surface cooling, and endovascular cooling w/ median pts temp 33C.<br><br>-Pts cooled within 6 hrs of symptom onset, antishiver agents utilized in 10 studies.<br><br>-Only one study cooled their patients for 48 hrs.<br><br>-This study did not fit the clinical question to this inquiry but assessed intervention options to improve pts outcomes. | I                    |

| Citation                                                                                                                                                                                                                                     | Purpose                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Sample/<br>Setting                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Design/<br>Framework                     | Variables/<br>Instruments                                                                                                                                                                                                                                                      | Results                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Implications                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Comments                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Level of<br>Evidence |
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| Lakhan, S...<br>et al. (2012).<br>Application<br>of mild<br>therapeutic<br>hypothermia<br>on stroke: A<br>systematic<br>review and<br>meta-<br>analyses.<br>Stroke<br>Research<br>and<br>Treatment.<br>1-12. doi:<br>10.1155/201<br>2/295906 | -“We aim to<br>collect solid<br>evidence to<br>define<br>whether<br>induced<br>hypothermia<br>is a useful<br>and safe<br>procedure<br>providing<br>long-term<br>benefits in<br>acute stroke<br>patients” (p.<br>2).<br><br>-“Summarize<br>all the<br>relevant<br>scientific<br>literature<br>coming from<br>available<br>clinical<br>studies on the<br>relation<br>between low<br>body<br>temperature<br>and post-<br>stroke<br>symptomato<br>logy” (p. 2).<br><br>- | -Search<br>performed<br>MEDLINE,<br>PubMed, &<br>Cochrane<br>databases;<br>study<br>selection<br>anything<br>before May<br>2011.<br><br>-17 articles<br>utilized (4<br>observational,<br>& 13 clinical<br>trials<br><br>-Exclusion<br>criteria: No<br>data reported<br>on patient<br>outcomes,<br>case reports,<br>review<br>papers, and<br>previous<br>meta-analyses<br><br>-Inclusion<br>criteria: post-<br>stroke pts that<br>received<br>hypothermia<br>treatment by<br>external or<br>internal<br>cooling. | -Systematic<br>Review &<br>Meta-analysis | -Clinical<br>outcomes: data<br>extraction on<br>number of<br>participants ,<br>population<br>characteristics,<br>intervention/group<br>selection, clinical<br>outcomes, and<br>mortality rate.<br><br>-NIHSS & mRS<br>assessed stroke<br>scales and<br>functional<br>outcomes. | -Clinical outcome<br>regarding stroke<br>severity when<br>comparing control<br>and hypothermia<br>group total Std.<br>mean difference -<br>0.17(95% {-<br>0.42,0.08} { $p=0.19$<br>}).<br><br>-Clinical outcome<br>regarding mortality<br>total risk ratio<br>1.6(95%CI{0.93,2.<br>78} { $p=0.09$ }).<br><br>-Stroke severity<br>heterogeneity:<br>$\text{Chi}^2=21.89, df=6, (p=0.001)$<br><br>-Mortality<br>heterogeneity<br>$\text{Chi}^2=2.88, df=5, (p=0.72)$ | -Evidence was not<br>significant<br>regarding<br>therapeutic<br>hypothermia in<br>post stroke<br>patients.<br><br>-There was a high<br>level of<br>heterogeneity<br>between studies<br>which may not<br>reflect the general<br>stroke patient<br>populations.<br><br>Limitations: There<br>was no limitations<br>section listed. The<br>study suggests mild<br>therapeutic<br>hypothermia in its<br>title but the studies<br>utilized mainly<br>used targeted<br>temperatures of<br>33C which is not<br>mild hypothermia. | -This study<br>does not fit<br>with clinical<br>question<br>proposed in<br>this review.<br><br>-The results of<br>this study<br>helps address<br>treatment<br>plans of stroke<br>patients that<br>develop fever.<br><br>-There needs<br>to be more<br>research on<br>targeted<br>temperatures<br>in stroke<br>patients tha<br>maintain<br>normothermia<br>or 36.5-37C.<br>Utilizing<br>intervention to<br>maintain<br>normothermia<br>and compare<br>that to<br>hyperthermia<br>pts may yield<br>benefit. | I                    |

| Citation                                                                                                                                                                                                                   | Purpose                                                                                                                                                                                                                                                                              | Sample/<br>Setting                                                                                                                                                                                                                                       | Design/<br>Framework                           | Variables/<br>Instruments                                                                                                                                                                                                                                                                                                                                                                  | Results                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Implications                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Comments                                                                                                                                                                                                                                                                                 | Level of<br>Evidence |
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| Leira, R., et al. (2006). Hyperthermia is a surrogate marker of inflammation-mediated cause of brain damage in acute ischemic stroke. Journal of Internal Medicine. 260(4), 343-349. doi: 10.1111/j.1365-2796.2006.01694.x | <p>-“Determine the potential relationship between proinflammatory markers and hyperthermia, as well as their relationship with increased brain damage” (p. 344).</p> <p>-Examine the relationships during AIS with proinflammatory cytokines and fever on neurological outcomes.</p> | <p>-Patient population included was first time AIS with new onset symptoms &lt; 24 hrs.</p> <p>-The sample size was 229 pts.</p> <p>-Setting was a prospective stroke data bank.</p> <p>-Exclusion criteria were infection or inflammatory diseases.</p> | -Prospective non-randomized comparative study. | <p>-Hyperthermia &gt; 37.5C, normothermia &lt; 37.5C.</p> <p>-Canadian Stroke Scale &lt; 7 was poor outcome and &gt; 7 good outcome.</p> <p>-Head CT performed at admission and 4-7 days.</p> <p>-Blood samples drawn at admission and 48 hrs (IL-6, TNF, ICAM-1, VCAM-1).</p> <p>-Outcome variables were infarct volume at 4-7 days and Canadian Stroke Scale assessment at 3 months.</p> | <p>-Hyperthermia was related to hyperglycemia, elevated fibrinogen, &amp; higher stroke severity at admission (<math>p&lt;0.0001</math>).</p> <p>-Hyperthermia was also related to higher infarct volume, early neurologic deterioration, &amp; higher stroke severity at 3 months with adjusted confounders (<math>p&lt;0.0001</math>).</p> <p>-Cytokines IL-6, TNF and ICAM-1 blood levels were elevated in hyperthermia group (<math>p&lt;0.001</math>).</p> <p>-Hyperthermia not independently associated with poor outcomes or larger infarct volume (<math>p&gt;0.05</math>).</p> | <p>-Hyperthermia was associated with poor neurological outcome at 3 months when proinflammatory markers were elevated.</p> <p>-Hyperthermia at 48 hrs was associated with elevated proinflammatory markers (IL-6, TNF, ICAM-1 and VCAM)</p> <p>-Hyperthermia at admission was associated with higher infarct volume at 48 hours.</p> <p>-38% of pts presented with hyperthermia at admission.</p> <p>-Limitations: No limitations section listed. Treatment of the hyperthermia group with antipyretics may have had effect on patient outcomes.</p> | -All pts w/ hyperthermia were treated with paracetamol or metamizole; only 9 pts (4.2%) presented w/ hyperthermia at 48 hrs. This may explain why hyperthermia was found to not be an independently associated poor neurological outcomes at three months and w/ larger infarct volumes. | IV                   |

| Citation                                                                                                                                                                                                                                                | Purpose                                                                                                                         | Sample/<br>Setting                                                                                                                                                                                                                           | Design/<br>Framework                                                                                                                                                                                                                | Variables/<br>Instruments                                                                                                                                                           | Results                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Implications                                                                                                                                                                                                                                                                                                    | Comments                                                                                                                                                                                                                                             | Level of<br>Evidence |
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| Middleton, S., et al. (2018). Vital sign monitoring following stroke associated with 90-day independence: a secondary analysis of the QASC cluster randomized. International Journal of Nursing Studies. 89, 72-79. doi: 10.1016/j.ijnurstu.2018.09.014 | -To examine links between 90-day dependence or death verse independence with regards to monitoring and treatment interventions. | -19 acute stroke units; 10 intervention hospitals and 9 control hospitals<br><br>-participants included pts with dx of AIS or ICH and admitted to stroke units within 48 hrs of stroke onset.<br><br>-970 patients were included with study. | -Single blinded randomized controlled trial<br><br>-10 interventional hospitals received treatment protocols for fever, sugar, and swallowing.<br><br>-9 control hospitals received existing national stroke management guidelines. | -Primary outcome measure was mRS at 90 days post stroke.<br><br>-mRS < 1 was considered independent.<br><br>-mRS > 2 was considered dependent<br><br>-Fever was considered > 37.5C. | -Pts who experienced one febrile event within the first 72 hrs of admission were found to have significantly lower odds of independence ( $p < 0.0001$ ).<br><br>-Higher mean temp was found to be associated with lower odds of independence ( $p < 0.0001$ ).<br><br>-Fever within the first 72 hrs that were treated with Acetaminophen were not associated improved independence ( $p > 0.05$ ).<br><br>-Limitations: No limitations sections listed within article. Treatment with Anti-pyretic treatment was only performed on 23% of pts that had a febrile event. | -Pts who develop a fever within the first 72 hrs of admission have a higher risk of dependence and mortality.<br><br>-Pts who have a higher mean temp that is > 37.5C have a higher risk of dependence and mortality.<br><br>-Pts who were treated with Acetaminophen were not shown to have improved outcomes. | -This study utilized a large sample size which was randomized which provided a high level of evidence for this inquiry.<br><br>-The treatment of fever with anti-pyretics needs further evaluation for efficacy due to poor intervention compliance. | II                   |

| Citation                                                                                                                                                                     | Purpose                                                                                                                                                                       | Sample/<br>Setting                                                                                                                                                                                                     | Design/<br>Framework            | Variables/<br>Instruments                                                                                                                                                                                                                                                                                               | Results                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Implications                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Comments                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Level of<br>Evidence |
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| Phipps, M., et al. (2011). Epidemiology and outcomes of fever burden among patients with acute ischemic stroke. Stroke. 42(12), 3357-3362. doi: 10.1161/STROKEAHA.111.621425 | -“Describe the patten of poststroke fever among hospitalized w/ AIS and examine the association between number of fever events and fever burden w/ stroke outcomes” (p. 3357) | -3 Veteran Affairs and 2 non-Veteran Affair hospitals.<br><br>-Data collected over a 5-year period<br><br>-N=1361 pts, & n=483 (febrile event)<br><br>-Inclusion criteria: AIS w/n 2 days of symptom onset, NIHSS > 2. | Retrospective comparative study | -Primary outcome: in-hospital mortality or discharged to hospice<br><br>-Temp > 37.8 (100.0F)<br><br>-Fever burden defined example 2 days of fever w/ a temp max 102F minus 100F multiplied by fever days ((102F-100F)x2days=4 degree-days).<br><br>-Fever burden (degree-days) 0.1-2.0 low, 2.1-4.0 medium, >4.0 high. | -Any fever episode OR 2.7(95%CI, 1.6-4.4), & number of fever episodes non-significant.<br><br>-Pts w/ fever 103/483 or 21.3 % of them died or were discharged to hospice compared w/ 37/878 or 4.2% of pts w/o fever (p<0.0001).<br><br>-Low-fever burden OR 1.2 (95%,CI,0.6-2.3, Medium OR 3.9(95% CI,1.9-8.2), & high OR 6.7(95%CI,3.6-12.7).<br><br>-Combined outcome w/ fever burden 4.2% no fever, 9.2% low, 24.7% medium, & 44.3% high (p<0.0001 trend). | -Fever occurs commonly in post-stroke and is associated with poor pts outcomes.<br>-High-fever burden has a six-fold increase in poor pts outcomes; this includes high-fever short period or low-grade fever for extended period.<br>-35% had temp 100-101F, 9.3% 101.1-102F, & 5.4% > 102F.<br>-19.9% low, 5.9% medium, & 9.6% high fever burden.<br>-12% had fever w/n 24 hrs, & 58% fever w/n 72 hrs.<br><br>Limitations: Temp were randomly recorded each day which may have missed peak temp measurements, Infection was not efficiently tracked, post-hoc analysis of previous study which did not address clinical question of this study. | -Early versus late febrile events showed non-significance with outcome (p=0.30)<br>-Early low-grade fevers for short periods (low burden) not associated with combined outcome OR 1.2(95%CI,0.7-2.2)<br>-Independently associated with outcome at admission, stroke severity, worsening symptom course, admission code status, length of stay, and hypoxia.<br>-Mean temp 101.1F, & mean number of days with fever 2.9.<br>-Average fever burden was 3.9 degree-days. | IV                   |

| Citation                                                                                                                                                                                                                        | Purpose                                                                                                                                                                                                                                                   | Sample/<br>Setting                                                                                                                                                                                                                                                                                                                                                  | Design/<br>Framework | Variables/<br>Instruments                                                                                                 | Results                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Implications                                                                                                                                                                                                                                                                                                                          | Comments                                                                                                                                                                                                       | Level of<br>Evidence |
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| Prasad, K., et al. (2010) Fever is associated with doubling of odds of short-term mortality in ischemic stroke: An updated meta-analysis. Acta Neurologica Scandinavica. 122(6), 404-408. doi: 10.1111/j.1600-0404.2010.01326.x | <p>-“To determine the size of independent effect of fever on the outcome of mortality within one month after AIS” (p. 404).</p> <p>-“Aim was to determine the association between fever and outcome, independent of age and stroke severity” (p.405).</p> | <p>-Search conducted with Medline and Cochrane library, date range 1990-2008.</p> <p>-Keyword search: stroke, pyrexia, fever, mortality</p> <p>-6 studies included totaling 2986 pts.</p> <p>-Inclusion criteria: AIS w/ in-hospital mortality or at 30 days.</p> <p>-Exclusion: No data provided w/ odds ratios from logistic regression or no mortality data.</p> | -Meta-analysis       | <p>-outcome measured was short-term mortality rates when fever is present in AIS.</p> <p>-Fever w/n the first 24 hrs.</p> | <p>-Short-term mortality OR 2.20 (95% CI 1.59-3.03, <math>P&lt;0.00001</math>)</p> <p>-Heterogeneity with fever and co-morbidities was non-significant (<math>p=0.28</math>)</p> <p>Limitations: No limitations section listed with this meta-analysis.</p> <p>Short-term mortality is not defined.</p> <p>Mortality measures with each study varied from in-hospital, and 30-days. Fever was defined differently in each study utilized from <math>&gt;37.4C</math> to <math>&gt;37.9C</math>.</p> | <p>-Fever occurring w/n the first 24 hrs of onset of AIS is associated with short-term mortality.</p> <p>-Fever is independent association of age, stroke severity or co-morbidity including diabetes, hypertension, hyperlipidemia.</p> <p>-Fever with AIS pts in the first 24 hrs will double the odds of short-term mortality.</p> | <p>- This meta-analysis closely resembles the clinical question proposed by this inquiry.</p> <p>-This study is a very high level of evidence and should carry persuasion with discussion of this inquiry.</p> | I                    |

| Citation                                                                                                                                                                        | Purpose                                                                                                                                                                                                                                                                                                        | Sample/<br>Setting                                                                                                                                                                                                    | Design/<br>Framework             | Variables/<br>Instruments                                                                                                                                                                                                | Results                                                                                                                                                                                                                                                              | Implications                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Comments                                                                                                                                                                                                                                                                                                                                                                           | Level of<br>Evidence |
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| Rincon, F., et. al. (2012). Relationship between temperature, hematoma growth, and functional outcome. Neurocritical care society. 18(1), 45-53. doi: 10.1007/s12028-012-9779-9 | -Assess temp at different stages in relation to hematoma growth and functional outcome.<br><br>-Fever is a common occurrence in ICH, if presence of fever is associated with ICH growth, fever is association w/ functional 90-day outcome and identify if fever is an independent predictor of poor outcomes. | -Virtual International Stroke Archive<br><br>-N=303<br><br>-Inclusion criteria: CT proven ICH w/n 6 hrs of symptom onset, follow-up CT scan at 72 hrs, baseline ICH scores, and functional outcome scores at 90 days. | Retrospective comparative study. | -Admission and follow up head CT scan at 72 hrs w/ ICH volume assessment.<br><br>-90 day mRS, & mRS>3 was considered poor functional outcome.<br><br>-Fever > 37.5 w/ daily temp recordings<br><br>-Admission ICH scores | -Hematoma growth was significant w/ fever at 24 and 72 hrs ( $P<0.05$ ) but not w/ fever at admission, 48 and 168 hrs.<br><br>-Poor functional outcome at 90 days was significant w/ fever at 24, 48, & 168 hrs ( $p<0.05$ ) but not w/ fever at admission & 72 hrs. | -Fever was a common occurrence in ICH and was independently associated with ICH volume expansion at 72 hrs and poor functional outcome at 90 days.<br>-Hematoma growth shows that it has relation to timing of fever.<br>-Hematoma growth r/t to atrial fibrillation, HTN, anticoagulation, INR.<br>-Independent predictors of fever, HTN, hematoma volume > 15 mL, presence of IVH at 72 hrs, infection, & hematoma growth > 33%<br>-Limitations: Single daily temp recordings may have missed peak temp Study was observational, post-hoc analysis of source trial for ICH. | -Poor functional outcome at 90 days was r/t age, diabetes, NIHSS, GCS, ICH score > 1, infection, INR, baseline hematoma volume > 15 mL at admission, IVH, & hematoma growth > 33%.<br><br>-Mean ICH score at admission was 1 which may have explained the non-significance of baseline temp<br><br>-2% baseline, 48% 24 hrs, 66% 48 hrs, 51% 72 hrs, & 2% 168 hrs developed fever. | IV                   |

| Citation                                                                                                                         | Purpose                                                                                                                                                                                                                                                                                                                                                                                | Sample/<br>Setting                                                                                                                                                          | Design/<br>Framework              | Variables/<br>Instruments                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Results                                                                                                                                                                                                                                                                                                                                                                                                           | Implications                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Comments                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Level of<br>Evidence |
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| Rocco, A., (2007). Monitoring after the acute stage of stroke. Stroke. 38(4), 1225-1228. doi: 10.1161/01.str.0000259659.91505.40 | <p>-“to determine which complications are the most frequent in subacute stage of stroke, how many are detectable by monitoring, and whether these complications influence pts outcomes” (pg. 1226).</p> <p>-“to date it is still not clear how long after a stroke pts remain unstable and should be treated and monitored in a stroke unit to achieve better outcome” (pg. 1226).</p> | <p>-University hospital sub-acute stroke unit.</p> <p>-Data collection over a 30-month period.</p> <p>-Pts included with study have had both AIS and ICH; <i>N</i>=261.</p> | -Prospective non-randomized study | <p>- NIHSS score was measure in- regards to stroke severity; NIHSS &lt; 5 (mild), 5-13 (moderate), and &gt; 13 or death (severe).</p> <p>-Changes in admission and discharge NIHSS was considered clinically significant.</p> <p>-fever was defined as &gt; 37.8C.</p> <p>-Monitored influences of stroke severity in relation to neurological and medical complications</p> <p>-Monitored for changes in NIHSS at hospital admission and discharge in relation to neurological and medical complications.</p> | <p>-Hyperthermia was associated with a change to a more severe class of stroke (<i>p</i>=0.0018).</p> <p>-Hyperthermia OR14.12 (95% CI, 6.01-33.2) was independently associated with a higher risk of mortality.</p> <p>-urinary infections, hypertension, hyperglycemia, and hypoxia where also medical complications that were associated with a change to a more sever class of stroke (<i>p</i>&lt;0.05).</p> | <p>-The research article found that pts who develop a fever &gt; 37.8C are associated with worsened pts outcomes.</p> <p>-This article also identified that temp &gt; 37.8C is associated with deterioration of clinical exam in- regards to NIHSS.</p> <p>-Hyperthermia was the most frequent complication with AIS and ICH</p> <p>-19% of total sample population developed hyperthermia and was most frequent complication found.</p> <p>-Prolonged monitoring in a sub-acute stroke unit may result in improvements in the benefits achieved by acute stroke units.</p> <p>-Limitations: No limitations section listed within the narrative.</p> | <p>-This article focused on post-acute care of pts that suffered AIS or ICH. It identified a need for continued stroke care monitoring after the acute stroke event.</p> <p>-Hyperthermia was the most frequent medical complications that developed in this stroke pts population.</p> <p>-69% of patients showed no change in deficit, 20% improved in NIHSS, and 11% deteriorated NIHSS score.</p> <p>-urinary infections, hypertension, hypoxia where also associated with poor pts outcomes.</p> | IV                   |

| Citation                                                                                                                                             | Purpose                                                                                      | Sample/<br>Setting                                                                                                                                                                                                               | Design/<br>Framework               | Variables/<br>Instruments                                                                                                                                                                                   | Results                                                                                                                                                                                                                                                                                                                                                                                           | Implications                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Comments                                                                                                                                                                                                                                                                                                              | Level of<br>Evidence |
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| Saini M., et al. (2009) Effect of hyperthermia on prognosis after acute ischemic stroke. Stroke. 40(9), 3051-3059. doi: 10.1161/STROKEAHA.109.556134 | -“Determine the effect of temperature, in relation to time, on outcome after AIS” (p. 3052), | -Data collected from Virtual International Stroke Trials Archive (no time frames of data collection discussed).<br><br>-N=5305<br><br>-Inclusion criteria: pts aged 18-103, AIS, fever recordings at 8, 24, 48, 72 hrs & 7 days. | -Prospective non-randomized study. | -Clinical outcome: 3-month functional outcome w/ mRS. (poor outcome mRS>2), & post-stroke mortality up to 90 days.<br><br>-Hyperthermia defined > 37.2C.<br><br>-NIHSS > 16 severe, & < 16 mild to moderate | -Hyperthermia at 8, 24, 48, 72 hrs, & 7 days were significant for poor long-term outcomes ( $p<0.05$ ) but not at baseline.<br><br>-HR for hyperthermia w/ 95% CI at baseline 1.2(1-1.4), 8 hrs 1.7 (1.2-2.2), 24 hrs 1.5(1.2-1.9), 48 hrs 2.0(1.5-2.6), 72 hrs 2.2(1.7-2.9), & 7 day 2.7(2.0-3.8).<br><br>-Hyperthermia at 8, 24, 48, 72 hrs & 7 days significant for poor outcome ( $p<0.05$ ). | -Likelihood of a poor outcome appeared to be greater the later the hyperthermia developed.<br><br>-Clinical characters that are significant to poor outcomes age > 70, NIHSS > 16, and tPA administration.<br><br>-Clinical characteristics that are associated with hyperthermia female, current smoker, ex-smoker, atrial fibrillation, NIHSS > 16, left hemispheric stroke, antibiotic utilization, WBC > 11.<br><br>Limitations: No consistent form of temp measurement, anti-pyretic or temp management intervention not accounted for in data, | -Greater infarction or lesion volume not associated with hyperthermia.<br><br>-Baseline hyperthermia not associated with poor outcomes.<br><br>-NIHSS > 16, lesion volume > 110mm & heart failure were associated w/ hyperthermia at 7 days ( $p<0.05$ ).<br><br>-stroke severity strongest predictor of hyperthermia | IV                   |

| Citation                                                                                                                                                                                                                                      | Purpose                                                                                                                                                                                                                                                                                                                                  | Sample/<br>Setting                                                                                                                                                                                                                                                                                                                                                                      | Design/<br>Framework                                                                                                                                                | Variables/<br>Instruments                                                                                                                                                                                                                                                                                                                         | Results                                                                                                                                                                                                                                                                                                                                 | Implications                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Comments                                                                                                                                                                                                                                                                                                                                                                                                                                  | Level of<br>Evidence |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------|
| Saxena, M., et al. (2015). Early temperature and mortality in critically ill patients with acute neurological diseases: trauma and stroke differ from infection. <i>Intensive Care Medicine</i> , 41, 823-832. doi: 10.1007/s00134-015-3676-6 | -The purpose of this study was to identify mortality rates in relation to fever with both stroke, TBI, and CNS infection and compare results.<br><br>-“elevated peak temp during the first 24 hours after ICU admission would be associated with increased mortality” in “TBI or stroke, but not in pts dx with CNS infection” (p. 824). | -all ICU pts admitted to 384 hospitals in Australia, New Zealand, and the United Kingdom; during time period 2005-2013.<br>-Inclusion criteria stroke, TBI, and CNS infection<br>-Exclusion criteria readmissions, cardiac arrest, missing vital signs data<br>-53,942 pts in Australia & New Zealand; 56,696 in the United Kingdom.<br>-TBI and Stroke N=83,717; CNS infection N=8,859 | Retrospective comparative study<br><br>-The data was extracted from two separate databases ANZICS-APD (Australia and New Zealand) and ICNARC-CMPD (United Kingdom). | -Primary outcome was in-hospital mortality<br><br>-peak temp as a categorical variable, divided into 0.5C increments<br><br>-Fever was defined as > 37.5C<br><br>-OR of peak temp were calculated for each increased increment in temp.<br><br>-TBI and stroke were combined because of consistency in findings of mortality in relation to fever | -United Kingdom in-hospital mortality peak temp 38.5-38.9C was OR 1.11(0.95-1.3), 39-39.4C OR 1.59(1.35-1.89), 39.5-39.9C OR 2.46(1.9-3.19), & >40C OR 6.67(4.7-9.4).<br><br>-New Zealand and Australia peak temp 38.5C-38.9C OR 1.11(0.97-1.25), 39-39.4C OR 1.62(1.34-1.96), 39.5-39.9C OR 1.94(1.4-2.67), & >40C OR 2.97(1.95-4.52). | -TBI and stroke pts are at a higher OR of -in-hospital mortality when temp is > 39C.<br><br>-Stroke and TBI were associated with increased mortality rate when below 37C and above 39C when compared to normothermia.<br><br>-Limitations: utilized a single peak temp not identifying patients that remained consistently > 37.5C; interventions for temp management was not accounted for within research tables or conclusion; age related differences were also not accounted for within research | -Sample population is only reflective of first 24 hours of admission.<br>-Study sample large which displays better assessment of the general public.<br>-Study did not draw discrepancies between patient populations that received targeted temp or hyperthermia treatment.<br>-Patient morbidities were not a unit of measure with this study.<br>-Mortality was measured at discharge and not distinguished at six months or one year. | IV                   |

| Citation                                                                                                                                                                                                         | Purpose                                                                                                                                                                                                                                                                                                                              | Sample/<br>Setting                                                                                                                                                                         | Design/<br>Framework            | Variables/<br>Instruments                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Results                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Implications                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Comments                                                                                                                                                                                                                                                                                                                                                                                                                             | Level of<br>Evidence |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------|
| Seo, W., et al. (2008). The impact of hyperthermia and infection on acute ischemic stroke patients in the intensive care unit. <i>Neurocritical Care Society</i> . 9(2), 183-188. doi: 10.1007/s12028-008-9056-0 | <p>-“We evaluated the impact of hyperthermia after an ischemic stroke on early patient outcomes” (p. 183).</p> <p>-“Determine the role of infection on the outcome of acute ischemic stroke patients admitted to the ICU by comparing patients with infectious hyperthermia to those with non-infectious hyperthermia” (p. 183).</p> | <p>-Tertiary teaching hospital admitted from 2004-2006.</p> <p>-N=150</p> <p>-Admitted within 24 hrs of AIS symptom onset</p> <p>-Hemorrhagic stroke pts were excluded from this study</p> | Retrospective comparative study | <p>-Normothermia (&lt;37.6C), mild hyperthermia (&gt;37.6-&lt;38C), and severe hyperthermia (&gt;38C).</p> <p>-Outcomes measured in-hospital mortality and LOS &gt; 4 days in the ICU.</p> <p>-Extended list of clinical risk factors that may relate to study outcomes.</p> <p>-Time to first hyperthermia &amp; duration of hyperthermia non-significant (<math>p=0.3</math>, <math>p=0.4</math>).</p> <p>-Infection was an independent predictor of increased LOS (<math>p&lt;0.001</math>).</p> | <p>-Severe hyperthermia vs normothermia OR 10.28(95%:CI:2-53) for in-hospital mortality &amp; 7.75(95%:CI:2.9-21) for increased LOS.</p> <p>-GCS, leukocytosis, infarction volume body temp, and endotracheal tube significantly associated w/ in-hospital mortality (<math>p&lt;0.05</math>)</p> <p>-HLD, GCS, elevated ESR, infarction volume, hyperthermia, &amp; endotracheal tube significantly associated w/ increased LOS (<math>p&lt;0.05</math>).</p> <p>-Mild hyperthermia compared to normothermia for increased LOS (<math>p=0.028</math>)</p> | <p>-Hyperthermia and GCS were independently related to increased LOS and in-hospital mortality rates.</p> <p>-Temp &gt; 38C related to increased mortality and increased LOS.</p> <p>-Temp &gt;37.6-&lt;38C related to increased LOS but not in-hospital mortality.</p> <p>-First recorded temp &gt; 37.6C and length of time hyperthermic not related to increased LOS or in-hospital mortality.</p> <p>-Limitations: Leukocytosis not related to infection with no discussion for rationale. Study design may misinterpret non-infection presence. Hyperthermia treatment not standardized.</p> | <p>-Infection present in 70% of pts with hyperthermia pneumonia was most common cause.</p> <p>-56 pts were hyperthermic (37%), Mean length of time for hyperthermia 23-25 hrs.</p> <p>-Mortality associated w/ ICU admission, GCS, NIHSS, leukocytosis, infarction volume, &amp; endotracheal tube.</p> <p>-Increased LOS associated with ICU admission, hyperlipidemia, GCS, NIHSS, infarction volume, &amp; endotracheal tube.</p> | IV                   |

| Citation                                                                                                                                                                                        | Purpose                                                                                                                                                                              | Sample/<br>Setting                                                                                                                                                                                                                                                                                                                | Design/<br>Framework     | Variables/<br>Instruments                                                                                                                                                                                                                  | Results                                                                                                                                                                                                                                                                                                                                                                                                  | Implications                                                                                                                                                                                                                                              | Comments                                                                                                                                                                                                                                                                                                                  | Level of<br>Evidence |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------|
| Wartenberg, K., et al. (2006). Impact of medical complications on outcome after subarachnoid hemorrhage. <i>Critical Care Medicine</i> . 34(3), 617-623. doi: 10.1097/01.ccm0000201903.46435.35 | -“We sought to determine the frequency of medical complications after subarachnoid hemorrhage and to identify complications that significantly contribute to poor outcome” (p. 618). | -Columbia University Medical Center; neurology intensive care unit, data collection over 6-year period.<br><br>-N=576<br><br>-Inclusion criteria: Aneurysmal or spontaneous non-aneurysmal subarachnoid hemorrhage<br><br>-Exclusion criteria: < 18 years old, traumatic subarachnoid hemorrhage, and arterio-venous malformation | Retrospective comparison | -Survival and functional outcome at 3 months<br><br>-Poor outcome considered mRS > 3 or death<br><br>-Clinical risk factors also measured<br><br>-Fever defined as > 38.3C.<br><br>-Admission scores w/ Hunt and Hess Scores, GCS, & NIHSS | -Fever most frequent complication 54%; considered significant (p=0.02) w/ OR 2.0(95%CI,1.1-3.4).<br><br>-78% developed medical complication considered significant (p<0.0001).<br><br>-Medical complications considered significant as a predictor of poor outcome; age >54 years, aneurysm size > 10mm, aneurysm re-bleed, infarction r/t vasospasm, fever, anemia (hgb < 9), & hyperglycemia (p<0.05). | -Subarachnoid mortality rates 21%, and 19% mRS > 3 at 3 months.<br><br>-Fever considered significant predictor to poor outcomes.<br><br>-Limitations: single-center design, study was retrospective which can help contribute to bias within the results. | -Fever was displayed with high prevalence with the study cohort.<br><br>-Patients who developed fever where treated with anti-pyretic’s & cooling blankets.<br><br>-Sub-arachnoid hemorrhage has high prevalence of mortality and poor functional outcome.<br><br>-Fever prevalence also very high with this study cohort | IV                   |

Note. Temp or temperature, ICU or intensive care unit, TBI or traumatic brain injury, CNS or central nervous system, dx or diagnosis, pts or patients, OR or odds ratio, HR or hazardous ratio, CI or confidence interval, AIS or acute ischemic stroke, ICH or intracerebral hemorrhage, IVH or intraventricular hemorrhage, HTN or hypertension, C or Celsius, mRS or modified Rankin Scale, NIHSS or National Institute of Health Stroke Scale Score, N or study sample size, n or cohort sample size, GCS or glasgow coma scale, LOS or length of stay, ADL or activities of daily living, DVT or deep vein thrombosis

**\*\*\*Type/Levels of Evidence**

**Level I:** Evidence from a systematic review or meta-analysis of all relevant RCTs or evidence-based clinical practice guidelines based on systematic reviews of RCTS or three or more RCTS of good quality that have similar results.

**Level II:** Evidence obtained from a least one well-designed RCT (large multi-center RCT)

**Level III:** Evidence obtained from well-designed controlled trials without randomization (quasi-experimental).

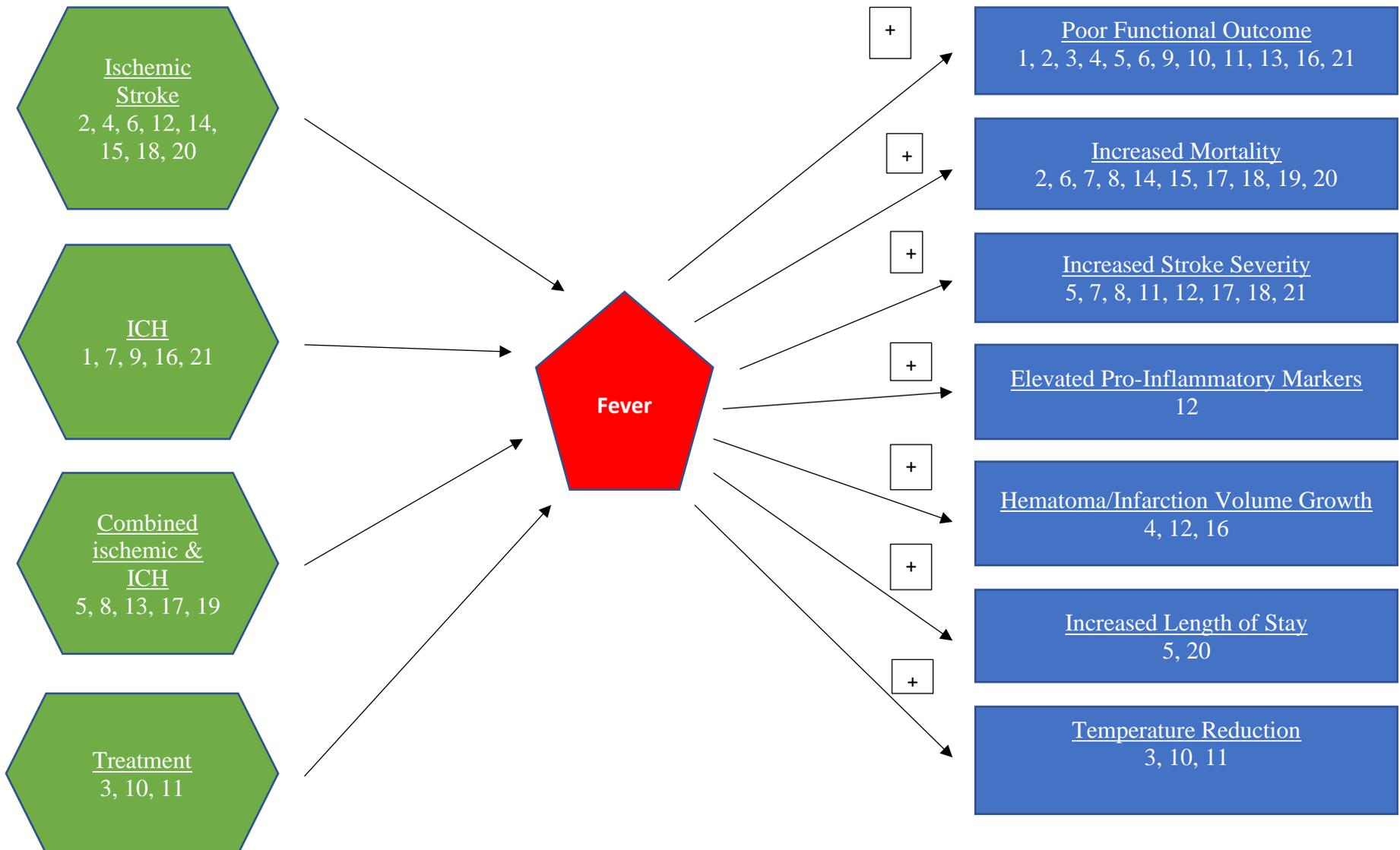
**Level IV:** Evidence from well-designed case-control or cohort studies.

**Level V:** Evidence from systematic reviews of descriptive and qualitative studies (meta-synthesis).

(Ackley, Swan, Ladwig, & Tucker, 2021)

## Appendix C

### Conceptual Map



**Conceptual Map Key**

+ : indicates positive relationship

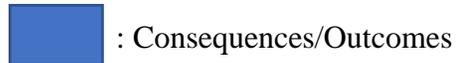
- : indicates negative relationship



: Antecedants



: Concept



: Consequences/Outcomes



: Indicates Relationship

1. Bush et al. (2018)
2. Diprose et al. (2020)
3. Fang et al. (2017)
4. Geurts et al. (2016)
5. Greer et al. (2008)
6. Hajat et al. (2000)
7. Honig et al. (2015)
8. Kammersgard et al. (2002)
9. Kramer et al. (2017)
10. Kucznski et al. (2020)
11. Lakhan et al. (2012)
12. Leira et al. (2006)
13. Middleton et al. (2018)
14. Phipps et al. (2011)
15. Prasada et al. (2010)
16. Rincon et al. (212)
17. Rocco et al. (2002)
18. Saini et al. (2009)
19. Saxena et al. (2015)
20. Seo et al. (2008)
21. Wartenberg et al. (2006)

## Appendix D

## 2019 AHA Guidelines for Acute Ischemic Stroke AGREE II Appraisal

| <b>Domain 1: Scope and Purpose</b><br><b>Domain Score: 19</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                       | <b>Strongly Disagree</b><br><b>1</b> | <b>2</b> | <b>3</b> | <b>4</b> | <b>5</b> | <b>6</b> | <b>Strongly Agree</b><br><b>7</b> |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------|----------|----------|----------|----------|----------|-----------------------------------|
| <p>1. The overall objective(s) of the guideline is (are) specifically described</p> <p><b>Comment:</b><br/>-The objective of this guideline is cited in the narrative; “the purpose of these guidelines is to provide an up-to-date comprehensive set of recommendations for clinicians caring for adult patients with acute arterial ischemic stroke” (p. 345).<br/>-This guideline will focus on arterial ischemic stroke in adults and secondary prevention measures in the first two weeks injury.</p>          |                                      |          |          |          |          |          | <b>X</b>                          |
| <p>2. The health questions(s) covered by the guideline is (are) specifically described.</p> <p><b>Comment:</b><br/>-The clinical question to the inquiry is discussed within this guideline. The guideline cited “peak temperature in the first 24 hours &lt;37C and &gt;39C was associated with an increased risk of in-hospital death compared with normothermia” (p. 361).<br/>-However, this guideline has remained unchanged since 2013 because of a lack of recent large multi-centered research studies.</p> |                                      |          |          |          |          | <b>X</b> |                                   |
| <p>3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.</p> <p><b>Comments:</b></p>                                                                                                                                                                                                                                                                                                                                                                        |                                      |          |          |          |          | <b>X</b> |                                   |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                              |                 |                 |                 |                 |                 |                                           |
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| <p>-The population is described within the narrative; the guideline cites “these guidelines address prehospital care, urgent and emergency evaluation and treatment with intravenous and intra-arterial therapies and in-hospital management, including secondary prevention measures that are often begun during initial hospitalization” (p. 345).</p>                                                                                                                                                                                                                                                                                          |                                              |                 |                 |                 |                 |                 |                                           |
| <p><b>Domain 2: Stakeholder Involvement</b><br/><b>Domain Score: 13</b></p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | <p><b>Strongly Disagree</b><br/><b>1</b></p> | <p><b>2</b></p> | <p><b>3</b></p> | <p><b>4</b></p> | <p><b>5</b></p> | <p><b>6</b></p> | <p><b>Strongly agree</b><br/><b>7</b></p> |
| <p>4. The guideline development group includes individuals from all the relevant professional groups.</p> <p><b>Comments:</b><br/>-The guideline discussed the writing group appointed to the AHA stroke council is representing various areas of medical expertise but when assessing the authoring group. Doctors where the majority with only a single Nurse represented in the authoring group from other professions.<br/>-The guideline lacked a diverse group of medical professionals that have experience managing care for this patient population.<br/>-This allows for diminished insight into the development of this guideline.</p> |                                              |                 |                 | <p><b>X</b></p> |                 |                 |                                           |
| <p>5. The views and preferences of the target population (patients, public, etc.) have been sought.</p> <p><b>Comments:</b><br/>-Nothing was noted within the guideline discussing subjective data on patient views or preferences<br/>-Unknown if views were sought</p>                                                                                                                                                                                                                                                                                                                                                                          |                                              | <p><b>X</b></p> |                 |                 |                 |                 |                                           |
| <p>6. The target users of the guideline are clearly defined.</p> <p><b>Comments:</b></p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                              |                 |                 |                 |                 |                 | <p><b>X</b></p>                           |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                       |                 |                 |                 |                 |                 |                                    |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|------------------------------------|
| <p>-The target users of the guideline were highlighted within the purpose of the article.</p> <p>-The guideline cited a “comprehensive set of recommendations for clinicians caring for adult patients with acute arterial ischemic stroke on a single document” (p. 47).</p> <p>-The guideline also cited “restricted our recommendations to adults and to secondary prevention measures that are appropriately instituted within the first two weeks” (p. 47).</p>                                                                                                                                                                                                                                      |                                       |                 |                 |                 |                 |                 |                                    |
| <p><b>Domain 3: Rigor of Development</b><br/> <b>Domain Score: 47</b></p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | <p><b>Strongly Disagree</b><br/>1</p> | <p><b>2</b></p> | <p><b>3</b></p> | <p><b>4</b></p> | <p><b>5</b></p> | <p><b>6</b></p> | <p><b>Strongly Agree</b><br/>7</p> |
| <p>7. Systematic methods were used to search for evidence.</p> <p><b>Comments:</b></p> <p>-There was an independent review board that was committed to performing a systematic review of the guidelines established within this article.</p> <p>-Named electronic databases, time periods, and search terms were not discussed within this article.</p> <p>-There are links to supplemental materials throughout the document that bring you to two documents. The documents contain evidence summary tables broken down by level of evidence of the study and literature search tables for each topic reviewed. In total there were 544 references including 17 guidelines from other organizations.</p> |                                       |                 |                 |                 |                 | <p><b>X</b></p> |                                    |
| <p>8. The criteria for selective the evidence is clearly described.</p> <p><b>Comments:</b></p> <p>-Adult patients who have had an arterial ischemic stroke were identified as the targeted patient population.</p> <p>-Study designs were listed within each individual designated guideline.</p>                                                                                                                                                                                                                                                                                                                                                                                                        |                                       |                 |                 |                 |                 | <p><b>X</b></p> |                                    |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |  |  |  |  |  |          |  |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|--|--|--|--|----------|--|
| <p>-Outcomes are also listed within each individual designated guideline which also are applied to the class recommendation.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |  |  |  |  |  |          |  |
| <p>9. The strengths and limitations of the body of evidence are clearly described.</p> <p><b>Comments:</b><br/>         -Does not exclusively list a limitations or strengths section.<br/>         -When relevant to each individual guideline appropriateness, outcomes, relevance, and benefit to the patient population are appropriately highlighted.</p>                                                                                                                                                                                                                                   |  |  |  |  |  | <b>X</b> |  |
| <p>10. The methods for formulating the recommendations are clearly described.</p> <p><b>Comments:</b><br/>         -The article cited “Draft recommendations and supporting evidence were discussed by the writing group, and the revised recommendations for each topic were reviewed by a designated writing group” (p. 346).<br/>         -The guideline also described each recommendation that was changed from the previous recommendation and also why it was changed with sources cited<br/>         -Group members then had to unanimously approve all recommendations with voting.</p> |  |  |  |  |  | <b>X</b> |  |
| <p>11. The health benefits, side effects, and risks have been considered in formulating the recommendations.</p> <p><b>Comments:</b><br/>         -The article within each individual guideline lists the data and outcomes that are relevant to each intervention.<br/>         - Yes, this is described by the class of recommendation and a description of the reasoning</p>                                                                                                                                                                                                                  |  |  |  |  |  | <b>X</b> |  |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |  |  |  |          |  |  |          |
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| <p>for the class if it has changed from the previous version of the guideline.<br/>         -However, the article does not list the benefits and side effects explicitly when applying the identified interventions within the guideline</p>                                                                                                                                                                                                                                                                                                                                                                             |  |  |  |          |  |  |          |
| <p>12. There is an explicit link between the recommendations and the supporting evidence.</p> <p><b>Comments:</b><br/>         -The body of evidence supporting each intervention within the guideline is listed and relevant to each individual guideline.<br/>         -There was also a class of recommendation listed within each intervention highlighting the level of evidence to support each individual guideline.</p>                                                                                                                                                                                          |  |  |  |          |  |  | <b>X</b> |
| <p>13. The guideline has been externally reviewed by experts prior to its publication.</p> <p><b>Comments:</b><br/>         -The guideline was expertly peer reviewed by fourteen individuals.<br/>         -There was also an oversight committee and stroke council leadership committee that was involved in reviewing the research and its application to each individual guideline.<br/>         -The guideline was also endorsed and reviewed by the Society for Academic Emergency Medicine, Neurocritical Care Society, American Association of Neurological Surgeons and Congress of Neurological Surgeons.</p> |  |  |  |          |  |  | <b>X</b> |
| <p>14. A procedure for updating the guideline is provided.</p> <p><b>Comments:</b><br/>         -This was not explicitly discussed.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |  |  |  | <b>X</b> |  |  |          |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                              |                 |                 |                 |                 |                 |                                           |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-------------------------------------------|
| <p>-The 2019 guidelines are an updated version of the 2018 stroke guidelines already established by the AHA and ASA.</p> <p>- The article cited “RCTs addressing arterial ischemic stroke published between November 2018 and April 2019 were reviewed by the writing group” (p. 345).</p>                                                                                                                                                                                                                                                                                                    |                                              |                 |                 |                 |                 |                 |                                           |
| <p><b>Domain 4: Clarity of Presentation</b><br/><b>Domain Score: 20</b></p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | <p><b>Strongly Disagree</b><br/><b>1</b></p> | <p><b>2</b></p> | <p><b>3</b></p> | <p><b>4</b></p> | <p><b>5</b></p> | <p><b>6</b></p> | <p><b>Strongly Agree</b><br/><b>7</b></p> |
| <p>15. The recommendations are specific and unambiguous.</p> <p><b>Comments:</b></p> <p>-The recommendations are clearly discussed within the article</p> <p>-The guideline discussed its target patient population and how to apply various stages of care to arterial ischemic stroke patients</p> <p>-The guideline recommendation that is specific to this inquiry is cited “sources of hyperthermia (temperature &gt; 38C) should be identified and treated, and antipyretic medications should be administered to lower temperature in hyperthermic patients with stroke” (p. 361).</p> |                                              |                 |                 |                 |                 |                 | <p><b>X</b></p>                           |
| <p>16. The different options for management of the condition or health issue are clearly presented</p> <p><b>Comments:</b></p> <p>-The guideline lists a detailed plan of care that should be followed with arterial ischemic stroke patients.</p> <p>-The guideline highlights that are specific to this inquiry are to treat hyperthermia with anti-pyretic medications and that induced hypothermia has not shown to benefit patient outcome.</p>                                                                                                                                          |                                              |                 |                 |                 |                 |                 | <p><b>X</b></p>                           |
| <p>17. Key recommendations are easily identifiable.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                              |                 |                 |                 |                 | <p><b>X</b></p> |                                           |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                              |                 |                 |                 |                 |                 |                                           |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-------------------------------------------|
| <p><b>Comments:</b></p> <ul style="list-style-type: none"> <li>-The guideline lists in Table 2 key guidelines, policies, and statements that are relevant to the management of arterial ischemic stroke</li> <li>-The guideline also has a section dedicated to listing specific guidelines depending on patient location, timing of stroke, treatment measures, and inpatient guidance for improved patient outcomes.</li> <li>-There was no explicit location with summary of recommendations that were new or changed and no summary or conclusion paragraphs.</li> </ul> |                                              |                 |                 |                 |                 |                 |                                           |
| <p><b>Domain 5: Applicability</b><br/><b>Domain Score: 11</b></p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | <p><b>Strongly Disagree</b><br/><b>1</b></p> | <p><b>2</b></p> | <p><b>3</b></p> | <p><b>4</b></p> | <p><b>5</b></p> | <p><b>6</b></p> | <p><b>Strongly Agree</b><br/><b>7</b></p> |
| <p>18. The guideline describes facilitators and barriers to its application.</p> <p><b>Comments:</b></p> <ul style="list-style-type: none"> <li>-There was no formal location in which facilitators and barriers to the guideline were listed.</li> <li>-The guideline lists several different platforms of arterial ischemic stroke care in which require advanced care; barriers to this level of care are not listed within the guideline.</li> </ul>                                                                                                                     |                                              | <p><b>X</b></p> |                 |                 |                 |                 |                                           |
| <p>19. The guideline provides and/or tools on how the recommendations can be put into practice.</p> <p><b>Comments:</b></p> <ul style="list-style-type: none"> <li>-The guidelines clearly establish different algorithms with the interventions provided. Intravenous alteplase administration is good example of this; listing criteria needed for administration including timing, imaging, and form of stroke.</li> <li>-The guideline has a master table listing criteria for treatment in many different formats of arterial ischemic stroke.</li> </ul>               |                                              |                 | <p><b>X</b></p> |                 |                 |                 |                                           |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                      |          |          |          |          |          |                                   |
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| -There was also no formal section dedicated listing tools regarding putting recommendations into practice.                                                                                                                                                                                                                                                                                                                                                                                                                    |                                      |          |          |          |          |          |                                   |
| 20. The potential resource implications of applying the recommendations have been considered.<br><br><b>Comments:</b><br>-There is no formal location where resource implications with outcomes is listed.                                                                                                                                                                                                                                                                                                                    | X                                    |          |          |          |          |          |                                   |
| 21. The guideline presents monitoring and/or auditing criteria.<br><br><b>Comments:</b><br>- Although, there is no formal location key recommendations are highlighted throughout the guideline.<br>-This includes process measures and clinical outcome criteria.<br>-The guideline discusses the monitoring of temperature should be routinely performed and patients with a temperature > 38C should be treated.<br>-Criteria for guideline implementation or adherence to the recommendation is not explicitly mentioned. |                                      |          |          |          | X        |          |                                   |
| <b>Domain 6: Editorial Independence</b><br><b>Domain Score: 13</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                            | <b>Strongly Disagree</b><br><b>1</b> | <b>2</b> | <b>3</b> | <b>4</b> | <b>5</b> | <b>6</b> | <b>Strongly Agree</b><br><b>7</b> |
| 22. The views of the funding body have no influences the content of the guideline.<br><br><b>Comments:</b><br>-The article cited "strict adherence to the AHA conflict-of-interest policy was maintained throughout the writing and consensus process" (p. 345).<br>-There is no detailed information regarding funding for the guideline, but it can be assumed this guideline was funded by the AHA.                                                                                                                        |                                      |          |          |          | X        |          |                                   |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                      |          |          |          |          |          |                                   |
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| <p>23. Competing interests of guideline development group members have been recorded.</p> <p><b>Comments:</b><br/>         -There was a review of group members listed with a disclosure questionnaire presented in a table format for each group member.<br/>         -The guideline cited “members were not allowed to participate in discussions or to vote on topics relevant to their relations with industry” (p. 345).</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                      |          |          |          |          |          | <b>X</b>                          |
| <p><b>Overall Guideline Assessment</b><br/> <b>Domain Score: 14</b></p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | <b>Strongly Disagree</b><br><b>1</b> | <b>2</b> | <b>3</b> | <b>4</b> | <b>5</b> | <b>6</b> | <b>Strongly Agree</b><br><b>7</b> |
| <p>1. Rate the overall quality of the guideline.</p> <p><b>Comments:</b><br/>         -Throughout the guidelines listed for arterial ischemic stroke it was easily transferrable into practice and established a clear plan for implementation into bedside care.<br/>         -The guidelines were supported a high level of evidence which included systematic reviews and randomized controlled trials.<br/>         -The guidelines also utilized a ranking system for the recommendations which correlated with the level of evidence that supported each intervention.<br/>         -The guidelines also listed the data and research guided each individual intervention.<br/>         -The article was peer reviewed and had an oversight committee that monitored the writing group.<br/>         -Summary and conclusion paragraphs were not provided and neither were methods of how to apply the recommendations.</p> |                                      |          |          |          |          |          | <b>X</b>                          |
| <p>2. I would recommend this guideline for use.</p> <p><b>Comments:</b><br/>         Yes! Overall, the guideline is a great tool for managing arterial ischemic stroke. The guidelines</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                      |          |          |          |          |          | <b>X</b>                          |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |  |  |  |  |  |  |  |
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| <p>have been consistently updated with the most recent and highest level of evidence available. The guidelines displayed the research in which guided each intervention. Allowing the viewer to assess how the guideline was developed. The article also created a ranking system which allowed the viewer to better understand the quality of evidence that supported each individual intervention. The guidelines are clear and easily transferrable into practice. However, the guideline does not apply recommendations for how to the guideline can be put into practice. It should also be mentioned that each individual recommendation is clearly identifiable and implementation into bedside practice would not be difficult to navigate. The overall score for the guideline is high and should be instituted into bedside practice for arterial ischemic stroke patient populations.</p> |  |  |  |  |  |  |  |
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## Appendix E

## European Stroke Organization guidelines for the management of temperature in patients with acute ischemic stroke Agree II Appraisal

| <b>Domain 1: Scope and Purpose</b><br><b>Domain Score: 21</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | <b>Strongly Disagree</b><br><b>1</b> | <b>2</b> | <b>3</b> | <b>4</b> | <b>5</b> | <b>6</b> | <b>Strongly Agree</b><br><b>7</b> |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------|----------|----------|----------|----------|----------|-----------------------------------|
| <p>1. The overall objective(s) of the guideline is (are) specifically described.</p> <p><b>Comment:</b><br/>           -The guideline cited “The aim of this Guideline document is to assist physicians treating patients with acute ischemic stroke in their clinical decisions with regard to the management of temperature” (p. 941)<br/>           -Title very clearly states objective within title “guideline for the management of temperature in patients with acute ischemic stroke” (p. 941).</p>                                                                                                                                                                                                                                                                                               |                                      |          |          |          |          |          | <b>X</b>                          |
| <p>2. The health question(s) covered by the guideline is (are) specifically described.</p> <p><b>Comment:</b><br/>           -The guideline clearly discusses three specific questions.<br/>           -“In hyperthermic patient with acute ischemic stroke, does treatment of hyperthermia compared with no treatment of hyperthermia improve functional outcome and/or survival” (p. 943).<br/>           -“In normothermic patients with acute ischemic stroke, does prevention of hyperthermia with antipyretics compared with no prevention of hyperthermia improve functional outcome and/or survival” (p. 943).<br/>           -“In patients with acute ischemic stroke, does induction of hypothermia compared with no induction of hypothermia improve functional and/or survival” (p. 946).</p> |                                      |          |          |          |          |          | <b>X</b>                          |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                      |          |          |          |          |          |                                   |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------|----------|----------|----------|----------|----------|-----------------------------------|
| <p>3. The populations (patients, public etc.) to whom the guideline is meant to apply is specifically described.</p> <p><b>Comments:</b><br/>-The population of interest is described as acute ischemic stroke patients.</p>                                                                                                                                                                                                                                                                                         |                                      |          |          |          |          |          | <b>X</b>                          |
| <p><b>Domain 2: Stakeholder Involvement</b><br/><b>Domain Score: 16</b></p>                                                                                                                                                                                                                                                                                                                                                                                                                                          | <b>Strongly Disagree</b><br><b>1</b> | <b>2</b> | <b>3</b> | <b>4</b> | <b>5</b> | <b>6</b> | <b>Strongly Agree</b><br><b>7</b> |
| <p>4. The guideline development group includes individuals from all relevant professional groups.</p> <p><b>Comments:</b><br/>-The working group was listed within the article as well as their disciplines (internists, neurologists, &amp; information specialists).<br/>-The working groups institutions were also listed within the guideline as well as their locations.<br/>-The working groups role was general consensus or agreement with guideline specifics.</p>                                          |                                      |          |          |          |          |          | <b>X</b>                          |
| <p>5. The views and preferences of the target population (patients, public, etc.) have been sought.</p> <p><b>Comments:</b><br/>-The views of the targeted patient populations were not defined within the article.<br/>-Perspectives were sought and priority topics were discussed during plenary session during the Karolinska Stroke Update Conference.<br/>-Guideline review was also performed by two separate external reviewers.<br/>-The guideline was approved by a committee and executive committee.</p> |                                      |          |          | <b>X</b> |          |          |                                   |
| <p>6. The target users of the guideline are clearly defined.</p> <p><b>Comments:</b></p>                                                                                                                                                                                                                                                                                                                                                                                                                             |                                      |          | <b>X</b> |          |          |          |                                   |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                      |          |          |          |          |          |                                   |
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| -Target users appear to be assumed and not clearly defined within guideline.<br>-Recommendations are clearly defined within the guideline to inform clinical decision making.                                                                                                                                                                                                                                                                                                                                          |                                      |          |          |          |          |          |                                   |
| <b>Domain 3: Rigor of Development</b><br><b>Domain Score: 53</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                       | <b>Strongly Disagree</b><br><b>1</b> | <b>2</b> | <b>3</b> | <b>4</b> | <b>5</b> | <b>6</b> | <b>Strongly Agree</b><br><b>7</b> |
| 7. Systematic methods were used to search for evidence.<br><br><b>Comments:</b><br>-The guideline listed all electronic databases utilized; Cochrane library, MEDLINE, EMBASE, & CINAHL<br>-Time periods in which research was searched was also listed.<br>-Search terms utilized included “free text terms used to describe each PICO topic”; they are also found in supplement material provided (p. 942).                                                                                                          |                                      |          |          |          |          |          | <b>X</b>                          |
| 8. The criteria for selecting the evidence are clearly described.<br><br><b>Comments:</b><br>-Level of evidence selection utilized for guideline support was randomized controlled trials, & systematic reviews/meta-analysis.<br>-Target patient population was acute ischemic stroke.<br>-Eligible study selection included “for each PICO question, two authors independently screened the titles and abstracts” for article selection.<br>-Criteria for selecting the evidence is located in supplement materials. |                                      |          |          |          |          |          | <b>X</b>                          |
| 9. The strengths and limitations of the body of evidence are clearly described.<br><br><b>Comments:</b><br>-Strengths and limitations are listed within guideline discussion                                                                                                                                                                                                                                                                                                                                           |                                      |          |          |          |          |          | <b>X</b>                          |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |  |  |  |          |  |  |          |
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| <p>-Strengths include level of evidence to support guideline recommendation (systematic reviews and randomized controlled trials), implementation of GRADE system to assess quality of research, &amp; explicit evaluation of functional outcomes</p> <p>-Limitations include the limited research available that is of high quality or high level of evidence; “ the currently available data about temperature management in acute ischemic stroke are limited and the strengths of the recommendations are there for weak” &amp; “the strength of the ESO recommendation is weak, which implies little evidence is needed to change the recommendation” (p. 946).</p> |  |  |  |          |  |  |          |
| <p>10. The methods for formulating the recommendations are clearly described.</p> <p><b>Comments:</b></p> <p>-Delphi scores were utilized to grade the quality of evidence according to the “GRADE methodology” (p. 942).</p> <p>-Strength of the recommendation was concluded by the working group consensus.</p> <p>-Voting process ‘for’ or ‘against’ the recommendations</p> <p>-Recommendation strength was graded as ‘strong’ or ‘weak.’</p>                                                                                                                                                                                                                       |  |  |  |          |  |  | <b>X</b> |
| <p>11. The health benefits, side effects, and risk have been considered in formulating the recommendations.</p> <p><b>Comments:</b></p> <p>-Functional outcome is the health benefit and/or survival which is the outcome of measure for each recommendation.</p> <p>-Side effects and reporting of risk verse benefit are not listed within guideline.</p>                                                                                                                                                                                                                                                                                                              |  |  |  | <b>X</b> |  |  |          |
| <p>12. There is an explicit link between the recommendations and the supporting evidence.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |  |  |  |          |  |  | <b>X</b> |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |  |  |  |  |  |  |          |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|--|--|--|--|--|----------|
| <p><b>Comments:</b></p> <ul style="list-style-type: none"> <li>-The guideline clearly describes the link between evidence utilized in support of their recommendation.</li> <li>-There is both a quality of evidence and strength in recommendation listed for each individual recommendation.</li> <li>-Tables are utilized to break down the research utilized in support of the evidence.</li> <li>-Narrative is provided to discuss why evidence was utilized in support of recommendation.</li> <li>-The supporting evidence can also be found in supplement materials.</li> </ul>                                        |  |  |  |  |  |  |          |
| <p>13. The guideline has been externally reviewed by experts prior to its publication.</p> <p><b>Comments:</b></p> <ul style="list-style-type: none"> <li>-The guidelines were externally reviewed by two different reviewers.</li> <li>-Approval for guideline publications was performed by a guideline committee and executive committee.</li> <li>-Details of external review criteria are listed within appendices in which are not listed within guideline.</li> <li>-External reviewer information can be found in the supplement materials.</li> </ul>                                                                 |  |  |  |  |  |  | <b>X</b> |
| <p>14. A procedure for updating the guideline is provided.</p> <p><b>Comments:</b></p> <ul style="list-style-type: none"> <li>-Procedures for updating guidelines are listed within article.</li> <li>-Implementation of the GRADE system for quality and level of evidence utilized.</li> <li>-Guidelines would not be published in single document but in several documents that focused on specific interests of acute ischemic stroke.</li> <li>-The guideline also calls for more high levels of evidence regarding temperature outcomes with acute ischemic stroke specifically randomized controlled trials.</li> </ul> |  |  |  |  |  |  | <b>X</b> |

| <b>Domain 4: Clarity of Presentation</b><br><b>Domain Score: 28</b>                                                                                                                                                                                                                                                                                 | <b>Strongly Disagree</b><br><b>1</b> | <b>2</b> | <b>3</b> | <b>4</b> | <b>5</b> | <b>6</b> | <b>Strongly Agree</b><br><b>7</b> |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------|----------|----------|----------|----------|----------|-----------------------------------|
| <p>15. The recommendations are specific and unambiguous.</p> <p><b>Comments:</b><br/>           -The recommendations are specific to each clinical question.<br/>           -The recommendations were targeted to acute ischemic stroke patients with an outcome measure of functional outcome and/or survival.</p>                                 |                                      |          |          |          |          |          | <b>X</b>                          |
| <p>16. The different options for management of the condition or health issue are clearly presented.</p> <p><b>Comments:</b><br/>           -Yes, treatment of hyperthermia, prevention of hyperthermia, and induction of hypothermia are clearly presented with regard to the management of fever in acute ischemic stroke patient populations.</p> |                                      |          |          |          |          |          | <b>X</b>                          |
| <p>17. Key recommendations are easily identifiable.</p> <p><b>Comments:</b><br/>           -Recommendations are clearly defined in regard to the clinical question.<br/>           -The recommendations are presented in clearly marked boxes for each PICO question.</p>                                                                           |                                      |          |          |          |          |          | <b>X</b>                          |
| <b>Domain 5: Applicability</b><br><b>Domain Score: 12</b>                                                                                                                                                                                                                                                                                           | <b>Strongly Disagree</b><br><b>1</b> | <b>2</b> | <b>3</b> | <b>4</b> | <b>5</b> | <b>6</b> | <b>Strongly Agree</b><br><b>7</b> |
| <p>18. The guideline describes facilitators and barriers to its application.</p> <p><b>Comments:</b><br/>           - Facilitators and barriers were not discussed within guideline.</p>                                                                                                                                                            |                                      |          | <b>X</b> |          |          |          |                                   |

|                                                                                                                                                                                                                                                                                                                                              |                                      |          |          |          |          |          |                                   |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------|----------|----------|----------|----------|----------|-----------------------------------|
| -Potential facilitators and barriers can also be implied as the guideline suggest more of a knowledge-based plan of care.                                                                                                                                                                                                                    |                                      |          |          |          |          |          |                                   |
| 19. The guideline provides and/or tools on how the recommendations can be put into practice.<br><br><b>Comments:</b><br>-Recommendations for implications into practice were not discussed within guideline.<br>-The guideline recommendations are clear and tools on how to be put into practice are not applicable                         |                                      |          | X        |          |          |          |                                   |
| 20. The potential resource implications of applying the recommendations have been considered.<br><br><b>Comments:</b><br>-Resource implications were not discussed within the guideline.<br>-The resources required imply knowledge-based concepts which are well defined within the recommendations.                                        |                                      |          | X        |          |          |          |                                   |
| 21. The guideline presents monitoring and/or auditing criteria.<br><br><b>Comments:</b><br>-Monitoring and/or auditing criteria were not discussed within the recommendation.<br>-Monitoring and auditing are not as applicable and can be measured by functional outcome and/or survival of patients who suffer from acute ischemic stroke. |                                      |          | X        |          |          |          |                                   |
| <b>Domain 6: Editorial Independence</b><br><b>Domain Score: 13</b>                                                                                                                                                                                                                                                                           | <b>Strongly Disagree</b><br><b>1</b> | <b>2</b> | <b>3</b> | <b>4</b> | <b>5</b> | <b>6</b> | <b>Strongly Agree</b><br><b>7</b> |
| 22. The views of the funding body have not influenced the content of the guideline.<br><br><b>Comments:</b>                                                                                                                                                                                                                                  |                                      |          |          |          |          | X        |                                   |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                               |   |   |   |   |   |                            |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------|---|---|---|---|---|----------------------------|
| <p>-The funding body was not listed in the guideline; it is presumed the funding body is the European Stroke Organization.</p> <p>-Potential conflicts of interests are listed in the supplemental material.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                               |   |   |   |   |   |                            |
| <p>23. Competing interests of guideline development group members have been recorded.</p> <p><b>Comments:</b><br/>-There was a review of group members and competing members listed within the supplement materials.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                               |   |   |   |   |   | X                          |
| <b>Overall Guideline Assessment</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | <b>Strongly Disagree</b><br>1 | 2 | 3 | 4 | 5 | 6 | <b>Strongly Agree</b><br>7 |
| <p>1. Rate the overall quality of the guideline.</p> <p><b>Comments:</b><br/><b>The guideline very clearly addresses the clinical questions proposed with its recommendations. The guidelines establish a clear link with evidence used in support of the guideline recommendations. The overall methodology is sound and made very clear to the reader regarding the established clinical questions designed for this guideline. The quality of the guideline is high with detailed discussion of both the current body of knowledge regarding the guideline clinical questions and with the recommendations suggested. The authors research is very transparent which allowed the reader to assess the quality of the recommendation.</b></p> |                               |   |   |   |   |   | X                          |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                               |   |   |   |   |   |                            |

## Appendix F

### Joint Commission National Quality Measures Modified Rankin Score (mRS)

**Definition:** The mRS is a six-point disability scale with possible scores ranging from 0 to 6.

**Values:**

0. The patient has no residual symptoms.
1. The patient has no significant disability; able to carry out all pre-stroke activities.
2. The patient has slight disability; unable to carry out all pre-stroke activities but able to look after self without daily help.
3. The patient has moderate disability, requiring some external help but able to walk without assistance of another individual.
4. The patient has moderately severe disability; unable to walk or attend to bodily functions without assistance of another individual.
5. The patient has severe disability; bedridden, incontinent, requires continuous care.
6. The patient has expired.

## Appendix G

### The Glasgow Outcome Scale

**Definition:** This Glasgow Outcome Scale is a five-point outcome measures scale for post neurological injury.

1. Death: Severe injury or death without recovery of consciousness.
2. Persistent vegetative state: Severe damage with prolonged state of unresponsiveness and a lack of higher mental functions.
3. Severe Disability: Severe injury with permanent need for help with daily living.
4. Moderate Disability: No need for assistance in everyday life, employment is possible but may require special equipment.
5. Low Disability: Light damage with minor neurological and psychological deficits

## Appendix H

### Barthel Index

**Definition:** The main aim is to establish degree of independence from any help, physical or verbal, however minor and for whatever reason.

|                   |                                                                                                                                                                                                                                      |
|-------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Feeding:</b>   | 0 = unable<br>5 = needs help cutting, spreading butter, etc., or requires modified diet<br>10 = independent                                                                                                                          |
| <b>Bathing:</b>   | 0 = dependent<br>5 = independent (or in shower)                                                                                                                                                                                      |
| <b>Grooming:</b>  | 0 = needs to help with personal care<br>5 = independent face/hair/teeth/shaving (implements provided)                                                                                                                                |
| <b>Dressing:</b>  | 0 = dependent<br>5 = needs help but can do about half unaided<br>10 = continent                                                                                                                                                      |
| <b>Bowels</b>     | 0 = incontinent (or needs to be given enemas)<br>5 = occasional accident<br>10 = continent                                                                                                                                           |
| <b>Bladder</b>    | 0 = incontinent, or catheterized and unable to manage alone<br>5 = occasional accident<br>10 = continent                                                                                                                             |
| <b>Toilet Use</b> | 0 = dependent<br>5 = needs some help, but can do something alone<br>10 = independent (on and off, dressing, wiping)                                                                                                                  |
| <b>Transfers</b>  | 0 = unable, no sitting balance<br>5 = major help (one or two people, physical), can sit<br>10 = minor help (verbal or physical)<br>15 = independent                                                                                  |
| <b>Mobility</b>   | 0 = immobile or < 50 yards<br>5 = wheelchair dependent, including corners, > 50 yards<br>10 = walks with help of one person (verbal or physical) > 50 yards<br>15 = independent (but may use any aid; for example, stick) > 50 yards |
| <b>Stairs</b>     | 0 = unable<br>5 = needs help (verbal, physical, carrying aid)<br>10 = independent                                                                                                                                                    |

## Appendix I

### Canadian Stroke Scale

**Definition:** Aids Clinicians to stroke deficit by quantifying neurological assessment

| <b>Mentation:</b>                |                    | <u>Score</u> |
|----------------------------------|--------------------|--------------|
| Level of consciousness           | Alert              | 3.0          |
|                                  | Drowsy             | 1.5          |
| Orientation                      | Orientated         | 1.0          |
|                                  | Disoriented/NA     | 0.0          |
| Speech                           | Normal             | 1.0          |
|                                  | Expressive Deficit | 0.5          |
|                                  | Receptive Deficit  | 0.0          |
| <b>No Comprehension Deficit:</b> |                    |              |
| Face                             | None               | 0.5          |
|                                  | Present            | 0.0          |
| Arm: Proximal                    | None               | 1.5          |
|                                  | Mild               | 1.0          |
|                                  | Significant        | 0.5          |
| Arm: Distal                      | None               | 1.5          |
|                                  | Mild               | 1.0          |
|                                  | Significant        | 0.5          |
| Leg: Proximal                    | None               | 1.5          |
|                                  | Mild               | 1.0          |
|                                  | Significant        | 0.5          |
| Leg: Distal                      | None               | 1.5          |
|                                  | Mild               | 1.0          |
|                                  | Significant        | 0.5          |
| <b>Comprehension Deficit:</b>    |                    |              |
| Face                             | Symmetrical        | 0.5          |
|                                  | Asymmetrical       | 0.0          |
| Arms                             | Equal              | 1.5          |
|                                  | Unequal            | 0.0          |
| Legs                             | Equal              | 1.5          |
|                                  | Unequal            | 0.0          |