Therapeutic Hypothermia and Paediatric Cardiac Arrest

A review of the literature

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The Purpose of This Review
I decided to write about the use of hypothermia in children with cardiac arrest, largely because of two events. First, I became interested in how hypothermia can be exploited as a medical intervention after an accident in Tromsø in 1999, where they managed to rescue a woman with a body temperature of 13.5 degrees. Today she is completely healthy, largely because of hypothermia protective effect on the brain. Second, we had a lecture by Marianne Thoresen at the third year at the medical school. She spoke about how she utilizes hypothermia as a treatment for asphyxia in neonates. As a result, I wrote this review.

Abstract
Cardiac arrest among children between 0-18 years old is not uncommon and accounts for almost 25% of paediatric mortality. The survival rate is low and the outcome of the survivors is poor. There are no studies that have proven beneficial effects of therapeutic hypothermia in children with cardiac arrest. Based on successful results in adults and neonates studies, it is a discussion whether or not we should recommend therapeutic hypothermia also in children with cardiac arrest. Nevertheless, because of lack of other treatments available and presumed adverse effects of therapeutic hypothermia, there are intensive care units that perform this therapy in children with cardiac arrest. Even The European Resuscitation Council Guidelines for Resuscitation in Paediatric life support and American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care recommend therapeutic hypothermia after paediatric cardiac arrest. It is not a strong recommendation because these guidelines were based on a weak knowledge base and lack of studies of high quality. It is difficult to compare children with adults and even within the group of paediatric patients. The aetiology and pathophysiology of cardiac arrest differ between children and adults, and generally, the strength of studies about this topic is low because of the heterogeneity among the patients and small sample size. Can we extrapolate the positive effects of therapeutic hypothermia found in studies of adults with CA and neonates with asphyxia to treat children with CA?
This review is based on searches in PubMed, Embase, The Cochrane Library and UpToDate. It will evaluate the effects of therapeutic hypothermia in children suffering from cardiac arrest published in the period 1950 to 2015. It will also discuss how this therapy is used in adults with cardiac arrest and neonates with asphyxia.

Conclusions:
Today there are no studies that have showed statistically significant effect of therapeutic hypothermia on the outcome among children with CA, nor any adverse effects. This together with lack of other curable treatment available, therapeutic hypothermia is recommended based on adults and neonates studies. There is a need to make good quality controlled studies on the topic in the future. This requires large intervention collaborative studies.

Keywords: Therapeutic hypothermia; Induced Hypothermia; Cardiac Arrest; Heart Arrest; Cardiopulmonary Arrest; Sudden Cardiac Arrest; Cardiopulmonary Resuscitation; Children; Paediatric; Adolescent; Infant; Newborn; Neonates.

Methods
Literature searches were conducted in PubMed, Embase, The Cochrane Library and UpToDate from September 2014 to October 2015. I searched for all kinds of articles that assessed the effectiveness of therapeutic hypothermia in children with cardiac arrest. The search limitations did not restrict articles based upon the year of publication, and the language restriction was confined to English, Norwegian, Danish and Swedish. I found 173 articles in PubMed, of these 48 relevant, one article in the Cochrane Library and 12 in Embase, of these four relevant. The UpToDate website “Sudden Cardiac arrest and Death in Children” was last updated in May 2015.

Background
Cardiac arrest (CA) among children between 0-18 years old is not uncommon and out of hospital cardiac arrest accounts for almost ¼ of paediatric mortality in Netherland [1].
Mortality among children experiencing CA is high, and the outcome among the survivors is poor with sequelae like neurological disabilities and lifelong need for
care. The reduced blood flow to the brain occurring during a CA leads to ischemic injury and thus the adverse outcomes. After an eventually successful resuscitation, injury can also occur due to sudden reperfusion of ischemic areas.

The effect of therapeutic hypothermia has been showed to improve outcomes in adults with CA and neonates with asphyxia. Compared to those two groups, CA within a paediatric population has a more heterogeneous aetiology. Most CA in adults results from myocardial infarction with a rapid onset, often due to ventricular fibrillation (VF) and ventricular tachycardia (VT), while this is a less common aetiology in the paediatric population. The leading cause of CA among children is asphyxia in 80-90% of the cases.

Therapeutic hypothermia has been used experimentally after perinatal asphyxia as early as in 1824 [2], and later in adults with CA in the 1950s [3]. From 1970 to 1980, therapeutic hypothermia as low as 30°C-31°C was used after asphyxia CA in nearly drowned children in many paediatric intensive care units [4, 5]. In the 1980s, clinical health care workers observed negative consequences associated with this therapy, like infections and increased mortality. Therefore the therapy was abandoned and after the study by Bohn et. al in 1986 [6] of drowned paediatric victims suggested that hypothermia afforded no improvement in outcome and increased infectious complications. This paper has a serious weakness in that the two groups compared were small and the lack of therapy standardization, such as differences in the depth and duration of cooling between patients within the treatment group (temperatures as low as 30°C-31°C for some patients and up to 13 days in length). From the 1990s randomized controlled trials showed that mild therapeutic hypothermia (32°C to 34°C) had a positive effect on the outcome and mortality among adults with CA [7, 8] and in cases with neonatal hypoxic ischemic encephalopathy[9, 10]. From that on it has been a further focus on investigation of the effects of therapeutic hypothermia on brain protection. A study from 2013 found no effect of target temperature management at 33°C compared to 36°C in adult patients with out of hospital CA[11].
**Epidemiology**
There are 0.5 to 20 per 100,000 person-years that suffer from sudden CA among children, adolescents and young adults [13]. The incidence of CA in the paediatric population in Denmark from 2000 to 2006 was between 1.1 and 1.5 per 100,000 person-years [14]. Compared to adults with CA, a Canadian study from 2009 showed that the incidence of paediatric out of hospital CA was 8.04 per 100,000 person-years versus 126.52 per 100,000 person-years for adults [13]. The huge differences in the incidence of children with CA between different studies reflect the heterogeneity of the group and different use of inclusion criteria. Regarding survival, the survival rate for children patients with CA has shown to be higher than in adult patients. In 2013, the American Heart Association published statistics of survival rates between adults and children with in-hospital CA: 23.9% (95% CI: 23.2%-24.6%) among adults and 40.2% (95% CI: 34.2%-46.2%) among children (http://www.heart.org/HEARTORG/General/Cardiac-Arrest-Statistics_UCM_448311_Article.jsp). Another study found that children and adolescents were twice as likely to survive compared to both infants (patients younger than one year of age) and adults (patients older than 18 years of age) [13].

**Aetiology**
The aetiology and pathophysiology of CA differ between children and adults [9, 10, 13]. The most common causes of out of hospital CA among infants and children are sudden infant death, drowning and trauma. Unexpected CA in a previously healthy child is uncommon compared to adults. 80-90% of the causes of paediatric CA result from asphyxia [15, 16], but in adults, ventricular fibrillation and primary ischemic cardiac disease are the predominant causes (Table) [17, 18].
**Table. Common causes of paediatric CA[19]**

<table>
<thead>
<tr>
<th>Category</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asphyxia</td>
<td>Sudden infant death syndrome (SIDS, usually &lt;8 months of age)</td>
</tr>
<tr>
<td></td>
<td>Drowning</td>
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<td></td>
<td>Acute respiratory illness</td>
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<td></td>
<td>Central apnoea</td>
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<td>Smoke inhalation</td>
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<td>Airway obstruction</td>
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<td>Hanging</td>
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<td>Circulatory</td>
<td>Sepsis</td>
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<td>Trauma</td>
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<td></td>
<td>Congenital heart disease</td>
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<td></td>
<td>Arrhythmia</td>
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<tr>
<td></td>
<td>Dehydration</td>
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<td></td>
<td>Myocarditis</td>
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<tr>
<td>Neurological dysfunction</td>
<td>Seizures</td>
</tr>
<tr>
<td></td>
<td>Intracranial hypertension</td>
</tr>
<tr>
<td>Other</td>
<td>Toxin ingestion [15]</td>
</tr>
</tbody>
</table>

**In hospital CA compared to out of hospital CA**

There is a difference in children suffering from out of hospital CA and in hospital CA. As a general rule, out of hospital CA has a higher mortality and more severe neurological outcome compared to in hospital CA [20].

A systematic review and meta-analysis done by Bistritz et al. found that survival to hospital discharge among children with out of hospital CA was 2%-12% compared to 27-51% in children with in hospital CA. Of these 76% of the patients with out of hospital CA had a poor neurologic outcome compared to 24% - 53% in children with in hospital CA [21].

The causes of CA also differ between in hospital CA and out of hospital CA, with respiratory causes as the predominant cause (72%) of out of hospital CA, and cardiac cause (73%) in patients with in hospital CA [20]. The patients with out of hospital CA have usually a better healthy baseline compared to those with in hospital CA, like any chronic pre-existing conditions (in hospital CA: 88%, out of hospital CA: 49%), e.g. congenital heart diseases (in hospital CA: 50%, out of hospital CA: 10%) [20].
Among the patients with in hospital CA, the CA`s in the units other than intensive care units are more similar to out of hospital CA. In both out of hospital CA and CA`s in the normal hospital wards, it is required to start standard cardiopulmonary resuscitation without easy accessible advanced equipment. They are also more un-witnessed compared to in hospital CA at intensive care units, and therefore contribute to the higher mortality rate. As a conclusion, studies have to be done separately when studying the effects of therapeutic hypothermia among paediatric patients with CA.

The use of hypothermia in the medicine

Hypothermia is widely used in medical care. It is used in cardiac surgery all over the world. When cooling the brain, the metabolic and oxygen requirement reduces. Then the blood flow can be completely interrupted if the hypothermia is sufficient enough. This offers surgeons time when they stop the heart during cardiac surgery [3, 22]. For example during cardiopulmonary bypass where the brain is protected during deep hypothermic circulatory arrest (DHCA), low flow bypass and anterograde cerebral perfusion (ACP) [23]. There are a lot of studies that have shown good effects of therapeutic hypothermia on neurobiological outcomes among neonates with hypoxic ischaemic encephalopathy [9, 10] and adults with CA [7, 8, 24]. Today there are both American and European guidelines that recommend therapeutic hypothermia if the child remains comatose after resuscitation, based on adults and neonatal studies [25, 26]. These recommendations were mainly based on two adult studies from 2002 that recommended mild therapeutic hypothermia (32°C-34°C) for respectively 12 and 24 hours [7, 8]. In 2013, Nielsen et. al did not find any effect regards to mortality, neurological outcome of target temperature management at 33°C compared to 36°C in adult patients with out of hospital CA [11]. Strengths of this study compared to previously studies that recommendations were based on, are adequately temperature control in both study groups and the use of a blinded neurologic prognosticator. Therefore, International Liaison Committee on Resuscitation (ILCOR) now recommends a constant target temperature between 32°C and 36°C for at least 24 hours for adult with CA (strong recommendation) [27].
In the case of neonatal asphyxia, the recommended treatment is still mild therapeutic hypothermia (33°C-34°C) for 72 hours [9, 10]. It is important to be aware that this therapy has to be initiated within 6 hours after the insult, and is therefore an emergency treatment [28].

There are currently no other treatment options that have shown to improve outcome other than therapeutic hypothermia after paediatric CA, and this supports the importance in investigating this topic [29, 30].

Because of the low incidence of CA in children, the conduction of studies investigating the outcomes of CA necessarily has to include a heterogeneous population [31]. The variables can be within different aspects of the event, for example aetiology, physiology and in hospital CA vs. out of hospital CA. The consequence is that it is difficult to make comparable groups and carry out a valid meta-analysis.

**The effects of therapeutic hypothermia**

Hypothermia affects several organ systems and physiological reactions, e.g. metabolism, cardiovascular, cerebral and respiratory system, haematology, and pharmacokinetics and pharmacodynamics [32]. The theory behind the effect of therapeutic hypothermia is that cerebral metabolism decreases by 6% for each 1°C decrease in temperature [33], which means reduced oxygen need and reduced CO₂ production, in other words a reduction in the need to breathe. Other effects are reduced production of free oxygen radicals, excitotoxic substances (e.g. glutamate which increases the intracellular concentration of calcium), and effects on the gene expression of protecting proteins in the death mechanism of apoptosis and necrosis [34]. With reduced metabolism follows reduced cardiac output, which reduces the demand on the cardiac cell machinery [16].

**Complications to the procedure of therapeutic hypothermia**

Every kind of treatment can harm the patient, and therapeutic hypothermia is not an exception.
Reported complications to therapeutic hypothermia in adults, are ventricular arrhythmias, infections, immunosuppression, electrolyte abnormalities, hyperglycaemia, pancreatitis, polyuria [35, 36] coagulation and hemodynamic disturbance [33, 37], pulmonary hypertension [38] and bradycardia [7, 9, 10, 36]. Heart rate is normally reduced with 10 beats per 1°C reduction. Bradycardia should not be considered to be pathologic because it is a physiologic reaction to hypothermia, which is the key point of the therapy. In 2010, the largest study reporting the use of therapeutic hypothermia after paediatric CA found that temperature below target range (32°C-34°C) was associated with increased mortality [16]. A temperature between 28°C and 31°C has been associated with atrial fibrillation and ventricular fibrillation [31].

However, most studies have not demonstrated an increase in adverse effects of therapeutic hypothermia when adjusted for risk factors [10, 39, 40]. Arrich et al showed that there were no increase in hemodynamic fluctuations, arrhythmias, infections, coagulopathy or electrolyte imbalance when they compared normothermic patients (37°C) with hypothermic patients (33+/- 1°C) [41]. In neonates, three large randomised trials did not report any significant differences in adverse effect between normothermia (37°C) and hypothermia treatment (33,5°C) lasting for 3 days [9, 10, 42].

Regarding infections, fever is a normal physiologic response as part of the host defensive system. It assists in several important ways: increased mobility and proliferation of leukocytes, enhanced leukocyte phagocytosis and endotoxin effects decreased. Hypothermia is therefore theoretically an immunosuppressant, but this is stronger linked to accidental hypothermia rather than controlled therapeutic cooling.

It is not only therapeutic hypothermia in itself that can harm the patients. In the therapeutic hypothermia procedure, you have to administer medications to prevent shivering that would otherwise result in stress and higher oxygen need. Sedative drugs used during the procedure can theoretically harm the child, in particular the immature brain. As we have seen, reduced body temperature affects drug metabolism and receptor function. More knowledge is needed regarding whether drug choice and administration should be changed during hypothermia treatment.
**Hyperthermia**
The adverse effects of hyperthermia (>38°C) on the nervous system after CA further support the value of mild hypothermic treatment. Hyperthermia will exacerbate the ischemic cell injury not only in vulnerable brain regions, but also in regions normally resilient to short periods of normothermic global ischemia. Therefore it is important to prevent hyperthermia in CA patients [43-45]. The European Resuscitation Council Guidelines for Resuscitation in paediatric life support recommends prevention of fever in children with cardiopulmonary arrest [25].

**Is it advisable to base the paediatric CA guidelines on adult and neonate studies?**
The answer is not obvious due to the fact that the aetiology and physiology differ between adults, children and neonates [9, 13, 29].

Differences in physiology between adults and children decrease as the child matures. This suggests that there are age dependent differences in response to different interventions that affects the physiology, e.g. therapeutic hypothermia. Children have a relatively larger body surface area compared to adults. This means a greater risk of loss of heat and fluid and uncontrolled temperature control. Another example is that the blood brain barrier is more immature in children. They may be more prone to develop neuronal damage from neuronal toxins as these cross the blood brain barrier more easily compared to in adults.

As we have seen, the leading causes of CA differ between ages. Children rarely have coronary ischaemic heart disease such as the cause of hypoxia compared to adults, but rather experience hypoxia from respiratory or neurological failure or shock [29]. Asystole and pulseless electrical activity (PEA) are also relatively much more common in children compared to adults who suffer more often from ventricular fibrillation [30, 40, 46]. The studies of adults with CA, are mainly based on ventricular fibrillation, and not asystole or pulseless electrical activity [29, 47]. Dumas et al 2011, concluded that therapeutic hypothermia in adults had no effect on the outcome in patients with asystole or pulseless electrical activity, but had desirable
effects on patients with ventricular fibrillation and ventricular tachycardia [47]. This means that therapeutic hypothermia in paediatric patients with CA, not necessary will benefit them as they more closely resembles the first group in the adult study population. On the other hand, there generally is a lower survival rate among patients that experience asystole or pulseless electrical activity independent of treatment (VT/VF: 20% vs. asystole/PEA: 5%) compared to patients with ventricular fibrillation or -tachycardia [13, 31].

The incidence of CA in non-public places is high in children, and decreases with age. Considering the importance of initiating therapeutic hypothermia within 6 hours after CA, this could interrupt with the effectiveness of therapeutic hypothermia in children suffering from CA [13].

Another important aspect of the protective effects of therapeutic hypothermia on the brain is that the brain in children is immature and constantly developing compared to in the adult. The continuum of the brain development results in age-differences in the responses to cerebral hypoxia [48]. The immature brain is more vulnerable to insults compared to a mature brain, and it can look like it is primed for apoptosis (apoptosis is essential for the brain development). The immature brain is more predisposed to delayed cell death, in addition to the primary injury [37, 49]. On the other hand, the immature developing brain has a greater ability of cell repair [50].

As opposed to CA in children (especially out of hospital CA), nearly all of the neonatal CAs are witnessed [48]. As a general rule, witnessed CAs have a higher survival rate compared to non-witnessed (16% compared to the overall survival rate of 8.6%) [30]. In addition, neonates with asphyxia have retained their blood supply to the brain for a longer time because of a beating heart before the asphyxia results in bradycardia, hypotension, and pulseless CA [29].

After CA, the brain in infants has more neuronal loss in the diencephalon, hippocampus, and the olivary bodies compared to older children and adults with more affection of the cerebral cortex. This is due to the fact that the cerebral cortex makes up a lower per cent of the total brain mass in infants compared to in older children. If the child survives, this can result in different clinical neurological symptoms, which
make it difficult to evaluate the effect of the treatment when comparing neonatal studies of therapeutic hypothermia with studies of older children treated with therapeutic hypothermia. As a consequence difficulties in extrapolating the clinical results from a neonate trial to a paediatric trial.

**Studies of children with CA**

Relevant studies about therapeutic hypothermia in children with CA have recently been widely discussed. Generally, the strength of these studies is low because of the heterogeneity among the patients and the small sample size. In 2014 Scholefield et. al found only two relevant retrospective studies and no randomised controlled trials (RCT) [16, 39]. However, the two study groups (therapeutic hypothermia-group, normothermia-group) were difficult to compare because the patients in the therapeutic hypothermia-group were sicker (higher incidence of chronic cardiac diseases, asphyxia and out of hospital CA). After adjusting for risk factors, there were no effects of therapeutic hypothermia on mortality (55.0% therapeutic hypothermia vs. 55.3% normothermia [16]), neurological outcome or complications associated with hypothermia (infections, arrhythmias, pulmonary oedema, bleeding). Their conclusion was that more studies are needed before new guidelines can be revised.

In 2013, Lin et al [36] found that the survival rate in the therapeutic hypothermia-group (78.6%) was higher than in the normothermia-group (46.4%), but this was at the time of hospital discharge and their study population were small. They used the Paediatric Cerebral Performance Category Scale (PCPC-scale) to measure the outcome. A score of <2 was more common in the therapeutic hypothermia-group compared to the normothermia-group (81.8% compared to 46.1%), but this was not statistical significant [51].

An article published in The New England Journal of Medicine in May 2015[18], showed that there was no significant difference in good outcome between the therapeutic hypothermia group and the normothermia-group among children with out of hospital CA. They used the outcome scale Vineland Adaptive Behavior Scales (VABS II), and a good outcome was above 70 (a scale from 20 to 160). It is a major weakness in the methodology. The percentage with a VABS-II score at 70 or above was 20% in the hypothermia group and 12% in the normothermia group. At the first glance, this looks like a huge effect. In spite of this, due to the small study sample
(138 in the hypothermia group and 122 in the normothermia group), the results aren’t statistically significant (CI 0.86-2.76). Strength of this study is that they exclusively studied children with OOH CA, which we have seen is of great importance for the outcome. Another strength of this paper was that they evaluated the outcome after 12 months compared to the patient’s condition before the CA. The baseline level before the CA did not differ between the two groups, and the drop in function after 1 year was almost the same. After one year 38% of the hypothermia group survived compared to 29% in the normothermia-group. There were also no differences in complications (infection, bleeding and serious arrhythmias). The mortality after 28 days was not different in the two groups.

**One on-going study**

Today it is one on-going, prospective, multicentre study about children with in hospital CA. Frank Moler (University of Michigan) and Michael Dean (University of Utah) are the principal investigators of this trial and the trial published in May 2015, which I have discussed above [18]. Compared to the article from May 2015, they now compare a group of pediatric patients with *in* hospital CA treated with therapeutic hypothermia (32°C-34°C) for 48 hours and then three days with normothermia (36°C-37,5°C), with five days of normothermia (ClinicalTrials.gov number NCT00880087). These two studies are unique in that they separately study in hospital CA and out of hospital CA, as we have seen that is highly relevant earlier in this text.

**Recommendations and guidelines**

Because of the low adverse effects of therapeutic hypothermia it is suggested that clinicians should use therapeutic hypothermia in all paediatric patients with CA where there is a possible chance for neurological injury [31]. However, there is not a clear consensus about this, because none of the trials has shown desired effect in paediatric patients. Based on adult and neonatal studies, The European Resuscitation Council Guidelines for Resuscitation in Paediatric life support [25] and American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care [26], recommend therapeutic hypothermia (32°C-34°C) if the child remains comatose after resuscitation. As we have seen earlier, from October 2015, ILCOR recommends a constant temperature between 32°C and 36°C in adult
patients [11, 27]. This may change the current international recommendation of 32°C-34°C in paediatric patients with CA.

Discussion
Neurological consequences after global hypoxic ischaemic damage of the brain in children presents with a wide spectrum; concentration and learning problems, cerebral palsy, blindness, hypothalamic and pituitary insufficiency and seizures [52].

The lack of comparable studies of therapeutic hypothermia in CA among children in addition to the lack of available treatment for CA means that there is a need of more research in this field. The studies need stricter inclusion criteria and standardization of protocols and procedures as of today there are no studies published or presented with a significant effect of therapeutic hypothermia in children with CA. This is in contrast to a series of studies in adults with CA and neonates with asphyxia. Because of the lack of other treatments available and lack of presumed adverse effects of therapeutic hypothermia, it is recommended to cool children based on adults and neonates studies.

A possible reason for the lack of proven effect from therapeutic hypothermia is the heterogeneity in the group of children with CA. The low incidence makes it difficult to have comparable groups with a sufficient number of patients, in contrast to CA in adults. As a result of this, a wide range of inclusion criteria have been implemented in the studies. Cases of asphyxia in neonates share a more common aetiology, and are thus a more homogeneous group. They are at the same age, have less chronic morbidities, often suffer from the same type of insult and do not have any other diseases or immunological conditions. This means that it is much easier to carry out good clinical trials with comparable groups both in neonates with asphyxia and adults with CA. EEG may be a method to use in studies of children with CA. It can be used to evaluate the degree of brain damage, and then make more comparable homogenous study groups and to increase the study quality.

The statistical analysis and quality of the follow-up examinations are as important as the treatment itself for the final result. The outcome analysis must be followed up for
many years to document possible long-term benefits from the treatment. This is especially important in children because of their ability to make huge improvement in abilities and skills as they grow. Their physiology is primed to develop, so the outcomes after 1 year are very uncertain predictors of long-term outcome. The first sign of a disability, and the effect of therapeutic hypothermia, can be seen when the expectations and requirements in performance increase, e.g. on school or at work. This will have a huge impact on the child’s quality of life. Further there is important to measure clinical relevant outcomes. There is a wide range from just manage to walk, compared to be able to go to school. A 3 level outcome scale with mild, moderate and severe is therefore not specific enough. With the use of Paediatric Glasgow Outcome Scale and PCPC, you can get more specific outcome measures [16, 36], and it has to be used not only at hospital discharge, but also in long-term follow-ups. Another scale to measure the outcome is VABS II. This scale measures a person’s level of everyday living skills, daily functioning and behaviour status. In this scale there are four adaptive behavioural domains composed of subdomains. I think this scale provide a good tool for the evaluation of the outcome in studies of children.

The economic aspect of studies of children can be a problem. Children have more years left to live than adults and it is therefore a good opportunity to do long-term follow-up studies to see weather or not the treatment is successful. It may be difficult to get the economic support for this including advanced neuropsychiatric testing and MRI examinations.

The ethical aspects are important as in any kind of research. Do we have the tools, knowledge and time to evaluate all sides that will matter for human functioning later in life? Are there undesirable consequences and complications of therapeutic hypothermia that we miss today, but will affect the children in a longer prospective?

As we have seen, there are mostly pros and few cons to hypothermic treatment, The short-term harm of therapeutic hypothermia has not been found to be statistically significant, but perhaps cooling and intensive care can do more harm than good to children that are actually too healthy to be treated with therapeutic hypothermia. Perhaps the brain damage we observe after the treatment, isn’t due to the primary insult, but a consequence of the treatment itself? And what is the optimal target
temperature? The challenge will be whether or not this specific patient should receive the treatment.

The planning of better multicentre trials with comparable study groups, standard protocols and equipment are important aspects of how we may be able to find groups of paediatric patients with CA that are comparable and may benefit from the therapeutic hypothermia.

**Conclusions**

Today there are no studies that have showed statistically significant effect of therapeutic hypothermia on the outcome among children with CA, nor any adverse effects. This together with lack of other curable treatment available, therapeutic hypothermia is recommended based on adults and neonates studies. There is a need to make good quality controlled studies on the topic in the future. This requires large intervention collaborative studies.
References


