Out-of-Hospital Cardiac Arrest – Transportation to Hospital and Early Predictors of Outcome

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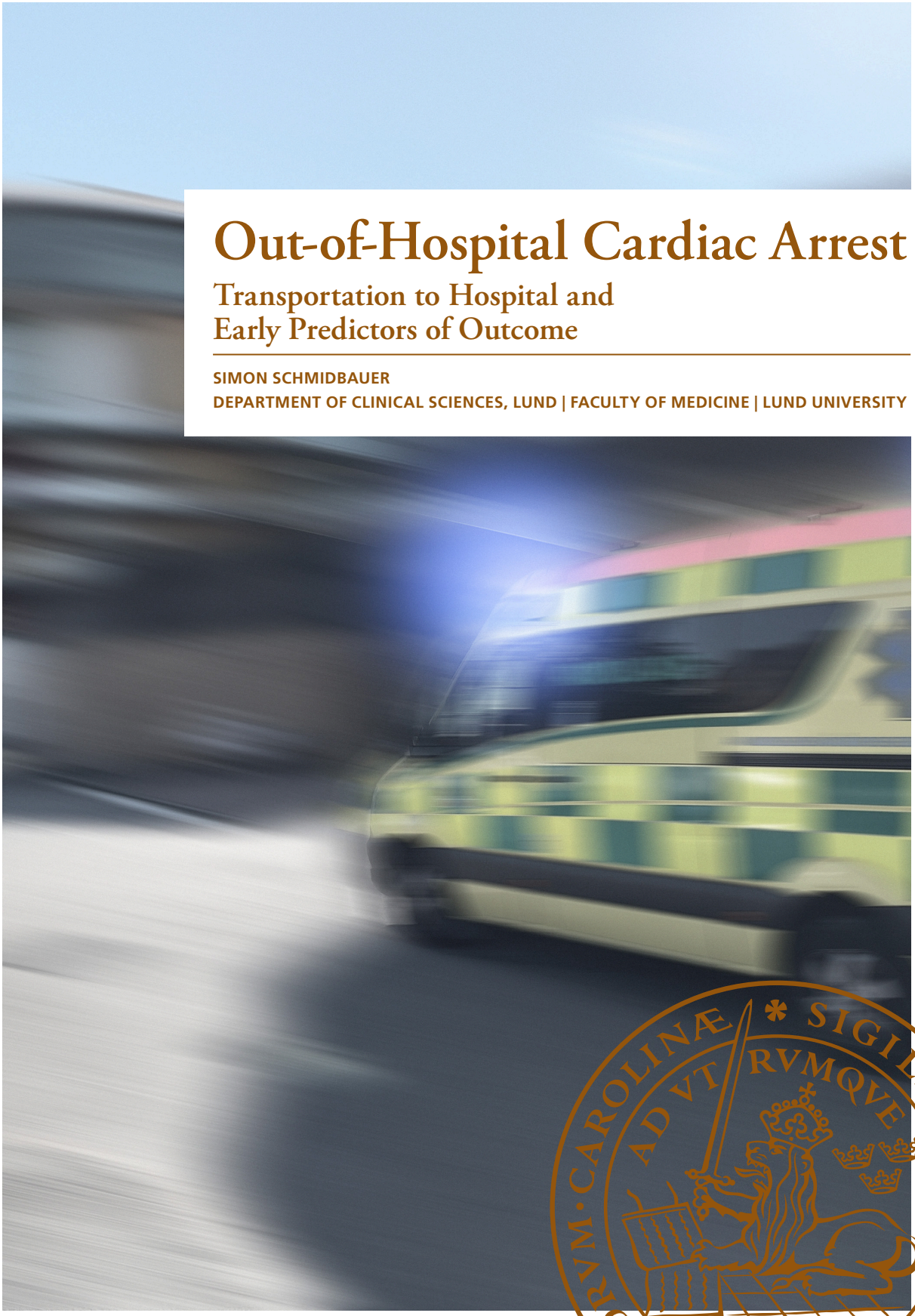

Out-of-Hospital Cardiac Arrest

Transportation to Hospital and Early Predictors of Outcome

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Simon Schmidbauer

LUND
UNIVERSITY

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Abstract

Automated chest compression (ACC) devices have not been shown to increase survival from out-of-hospital cardiac arrest (OHCA) and are not recommended for routine use in current resuscation guidelines, but they offer practical advantages especially when transporting patients with ongoing cardiopulmonary resuscitation (CPR). Outcomes for patients transported with ongoing CPR have, however, been reported to be poor and it is insufficiently studied whether transport with ongoing CPR is associated with the provision of any potentially life-saving in-hospital interventions prior to or after return of spontaneous circulation (ROSC). Several clinical decision rules (CDRs) and risk prediction scores have been proposed to guide decisions on termination of resuscitation or indicate futility of advanced therapies such as coronary angiography and mechanical circulatory support.

Paper I: An analysis of a large, nationwide registry including 24316 patients where factors associated with the use of ACC devices were studied in patients with OHCA in Sweden during the years 2011 through 2015. Unadjusted 30-day survival rate was 6.3 % for ACC patients. Markers of prolonged resuscitation attempts including drug administration and endotracheal intubation were more frequent among patients treated with an ACC-device. In a propensity score matched analysis, the odds ratio regarding 30-day survival for patients treated with an ACC device was 0.72 (95 % CI 0.62–0.84, $p < 0.001$).

Paper II: A retrospective cohort study including 409 patients who were transported to Skåne University Hospital, Lund, Sweden with ongoing CPR between 2010-2015. Seven patients (1.7 %) survived to hospital discharge, of whom three received an intervention against a suspected reversible cause of cardiac arrest prior to achieving sustained ROSC. The universal termination of resusctiation rule (consider termination if no ROSC prior to transport, arrest not crew-witnessed and no shocks delivered) would have prevented transport in 124 patients (30 %), including 2 who eventually survived – yielding a specificity of 71.4 % and a positive predictive value of 98.4 % (95 % CI 94.9–99.5 %).

Paper III: A retrospective cohort study including 227 patients transported to one of three acute hospitals in West Midlands, UK during a 14-month period 2016-2017. Three patients (1.3 %) survived to hospital discharge. The uTOR would have prevented transport in 89 cases (39.2 %), none of whom survived – yielding a specificity of 100 % and a positive predictive value of 100 % (95% CI 97.6–100.0%). In-hospital interventions were rare.

Paper IV: A *post-hoc* analysis of the large, international, multicentre TTM-2 trial including all patients with data on functional outcome at 6 months (n = 1829) comparing the well-validated Out-of-Hospital Cardiac Arrest (OHCA) and Cardiac Arrest Hospital Prognosis (CAHP)-scores to the less complex MIRACLE2- and Target Temperature Management (TTM)-scores. Discriminatory was excellent for the CAHP, MIRACLE2 and TTM-scores with areas under the receiver operation characteristics curve (AUROC) exceeding 0.8 with that of the OHCA score slightly lower.

Key words: Out-of-hospital cardiac arrest; Mechanical chest compression devices; Termination of resuscitation; Risk predicition; Transport with ongoing resuscitation

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"Death is not the enemy, but occasionally needs help with timing" *–Peter Safar's "Laws for the Navigation of Life, No. 20"*

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1 List of publications

This thesis is based on the following papers, which are referred to in text by their Roman numerals:

I) **Schmidbauer S**, Herlitz J, Karlsson T, Axelsson C, Friberg H. Use of automated chest compression devices after out-of-hospital cardiac arrest in Sweden. Resuscitation. 2017 Nov;120:95-102.

II) **Schmidbauer S**, Yates EJ, Andréll C, Bergström D, Olson H, Perkins GD, Friberg H. Outcomes and interventions in patients transported to hospital with ongoing CPR after out-of-hospital cardiac arrest - An observational study. Resusc Plus. 2021 Oct 16;8:100170.

III) Yates EJ, **Schmidbauer S**, Smyth AM, Ward M, Dorrian S, Siriwardena AN, Friberg H, Perkins GD. Out-of-hospital cardiac arrest termination of resuscitation with ongoing CPR: An observational study. Resuscitation. 2018 Sep;130:21-27.

IV) **Schmidbauer S**, Rylander C, Cariou A, Wise MP, Thomas M, Keeble TR, Erlinge D, Haenggi M, Wendel-Garcia PD, Bělohlávek J, Grejs AM, Nielsen N, Friberg H, Dankiewicz J. Comparison of four clinical risk scores in comatose patients after out-of-hospital cardiac arrest – a post-hoc analysis of the TTM2-trial. [Submitted manuscript]

2 Publications not included in thesis

- Dankiewicz J, Cronberg T, Lilja G, Jakobsen JC, Levin H, Ullén S, Rylander C, Wise MP, Oddo M, Cariou A, Bělohlávek J, Hovdenes J, Saxena M, Kirkegaard H, Young PJ, Pelosi P, Storm C, Taccone FS, Joannidis M, Callaway C, Eastwood GM, Morgan MPG, Nordberg P, Erlinge D, Nichol AD, Chew MS, Hollenberg J, Thomas M, Bewley J, Sweet K, Grejs AM, Christensen S, Haenggi M, Levis A, Lundin A, Düring J, **Schmidbauer S**, Keeble TR, Karamasis GV, Schrag C, Faessler E, Smid O, Otáhal M, Maggiorini M, Wendel Garcia PD, Jaubert P, Cole JM, Solar M, Borgquist O, Leithner C, Abed-Maillard S, Navarra L, Annborn M, Undén J, Brunetti I, Awad A, McGuigan P, Bjørkholt Olsen R, Cassina T, Vignon P, Langeland H, Lange T, Friberg H, Nielsen N; TTM2 Trial Investigators. Hypothermia versus Normothermia after Out-of-Hospital Cardiac Arrest. N Engl J Med. 2021 Jun 17;384(24):2283-2294.
- Friberg N, **Schmidbauer S**, Walther C, Englund E. Skeletal and soft tissue injuries after manual and mechanical chest compressions. Eur Heart J Qual Care Clin Outcomes. 2019 Jul 1;5(3):259-265.
- Bergström M, **Schmidbauer S**, Herlitz J, Rawshani A, Friberg H. Pulseless electrical activity is associated with improved survival in out-of-hospital cardiac arrest with initial non-shockable rhythm. Resuscitation. 2018 Dec;133:147-152.
- Dankiewicz J, **Schmidbauer S**, Nielsen N, Kern KB, Mooney MR, Stammet P, Riker RR, Rubertsson S, Seder D, Smid O, Sunde K, Søreide E, Unger BT, Friberg H. Safety, feasibility, and outcomes of induced hypothermia therapy following in-hospital cardiac arrest-evaluation of a large prospective registry*. Crit Care Med. 2014 Dec;42(12):2537-45.

3 Abbreviations

ACC: Automated chest compressions

AED: Automated external defibrillator

AHA: American heart association

AUROC: Area under the receiver operating characteristics curve

CAD: Coronary artery disease

CAHP: Cardiac arrest hospital prognosis

CDR: Clinical decision rule

CPR: Cardiopulmonary resuscitation

ECG: Electrocardiogram

ECMO: Extracorporeal membrane oxygenation

eCPR: Extracorporeal cardiopulmonary resuscitation

EMS: Emergency medical services

ERC: European resuscitation council

FPR: False-positive rate

ICU: Intensive care unit

IHCA: In-hospital cardiac arrest

ILCOR: International Liaison Committee on Resuscitation

LUCAS: Lund University Cardiac Assist System

OHCA: Out-of-hospital cardiac arrest

PCI: Percutaneous coronary intervention

SCRR: Swedish Cardiopulmonary Resuscitation Registry

TOR: Termination of resuscitation

TTM: Targeted temperature management

uTOR: Universal termination of resuscitation rule

4 Introduction

4.1 Cardiac arrest

A sudden thump. She rushes to kitchen and finds her husband on the floor. He is non-responsive and seems to gasp for air a few times before his breathing stops altogether. The emergency dispatcher quickly recognises his condition and encourages the wife to start bystander CPR while waiting for a nearby ambulance crew.

Shortly thereafter, a few houses down the road, another man drifts in and out of consciousness. His wife is also by his side, but unlike her neighbour, she is not alarmed by her husband's slowing, irregular breathing. His illness has slowly progressed over the last months, and during the last hospital visit it became clear that nothing more could be done to prevent the inevitable.

By definition, both these fictive scenarios depict men who with their loss of consciousness and absent or abnormal breathing - sustained a *cardiac arrest*.[1] Yet, many would agree that while one represents a medical emergency, where resuscitative measures can be the difference between certain death and return to life as it was, the other might be the natural end to a progressive illness.

In clinical practice, cases as clear as these are somewhat rare – cardiac arrest patients rather tend to present somewhere along a scale between these two extremes. Navigating this continuum and doing *everything* for patients who might benefit from it while having the courage to provide nothing but comfort for those who will not, is one of the great challenges in emergency medicine and critical care. This thesis will attempt to provide some guidance on this complex and sensitive subject by exploring therapies and objective measures associated with outcomes after out-of-hospital cardiac arrest (OHCA).

4.1.1 Causes of cardiac arrest

While cardiac arrest by both implication and definition is a *"cessation of mechanical cardiac activity",*[2] its recognition seldom involves any assessment of cardiac activity itself. Rather, it is the absence of signs of circulation which make the diagnosis.[3] Cardiac arrest is therefore better thought of as a clinical feature of severe circulatory failure leading to global cerebral ischemia, than a condition of itself.

Bearing this in mind, resuscitative measures cannot focus only on attempting to temporarily restore normal physiology – the underlying cause must be addressed as well.

Heart disease is the most common such underlying cause, with coronary artery disease (CAD) being the dominant subtype.[4] Acute coronary syndromes have the potential to cause malignant arrythmias through either transient ischemia/reperfusion or manifest occlusions with resulting myocardial infarction.[5] Patients with chronic manifestations of CAD are also at risk for life-threatening arrythmias, due to myocardial scar tissue providing substrates for ventricular reentry circuits.[6] Less commonly, structural heart disease of other causes or cardiac channelopathies might be the cause of cardiac arrest.[7]

Aetiologies of arrest outside primary heart disease span a broad spectrum of conditions, including sepsis, trauma, intoxication, and asphyxiation. Data from the Swedish Cardiopulmonary Resuscitation Registry (SCRR) indicate that pulmonary disease is the leading presumed non-cardiac cause of out-of-hospital cardiac arrest – although with some caveats regarding presumed causes of arrest which are outlined in the next section.

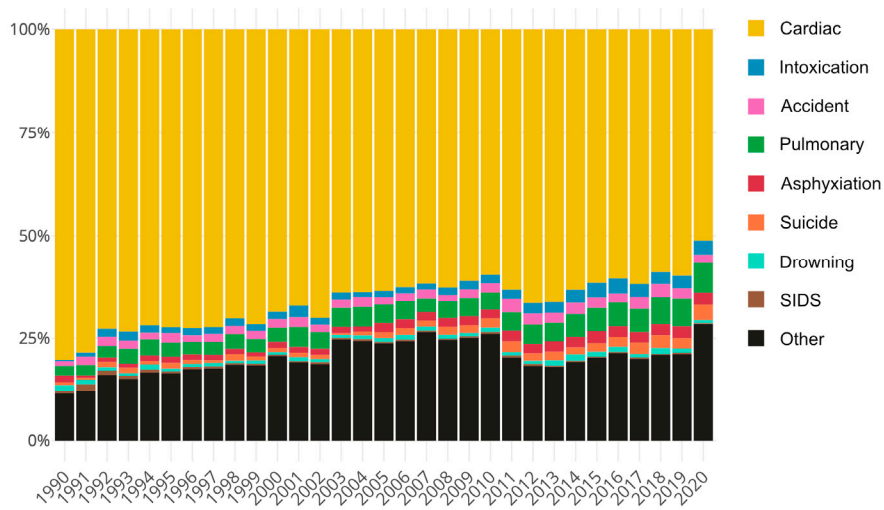

Figure 1. Presumed cause of out-of-hospital cardiac arrest. Translated from Swedish Cardiopulmonary Resuscitation Registry annual report 2021.[8] SIDS: Sudden infant death syndrome.

4.1.2 Classification of cardiac arrest

4.1.2.1 Presumed cause of arrest

A distinguishing feature of cardiac arrest over many other medical emergencies is its extreme time sensitivity. Therefore, the true cause of arrest – as outlined above – is seldom known during resuscitation where therapy has priority over diagnostics. Instead, decisions in this phase must be made from presumptions based on likelihood and clinical judgement. Simplifications such as the traditional dichotomisation of cardiac arrest into groups of *presumed cardiac* causes and *presumed non-cardiac* causes[9] could therefore be said to have evolved out of necessity, but rarely tell the whole truth.[10,11]

In the current version of the *Utstein* international consensus guidelines for uniform reporting of data from out-of-hospital cardiac arrest, a new category of *presumed medical* aetiology has been introduced. Acknowledging that only obvious non-cardiac causes of arrest (e.g. trauma, drowning, drug overdose) are likely to be recognised as such in the emergency setting, the *medical* category encompasses both presumed cardiac causes, other medical aetiologies and cases where the cause of arrest is unknown.[3] Whether or not this will improve uniform reporting remains to be seen, but from the Swedish Cardiopulmonary Resuscitation-registry (SCRR) it is clear that the aetiology will be classified as medical in a very wide range of patients using this definition.[12]

4.1.2.2 Initial rhythm

The initial ECG-rhythm, usually recorded upon the first defibrillator connection, is arguably the most objective and important clinical finding in the emergency setting of cardiac arrest. It determines the course of treatment during resuscitation (defibrillation vs. no defibrillation), carries great prognostic value[13–15] and offers clues about the underlying aetiology.[16,17]

Principally, four ECG-rhythms are recognised in cardiac arrest: *Ventricular fibrillation* (VF), *(pulseless) ventricular tachycardia* (VT), *pulseless electric activity* (PEA) and *asystole*. The first two, VT and VF are often combined to form one entity of *shockable* rhythms due to their equally favourable response to electrical defibrillation. Consequently, PEA and asystole tend to be classified as *non-shockable* rhythms, but unlike their shockable counterparts, those two rhythms have different prognostic implications.[18] It might therefore be better to consider these as separate entities.

As rhythms evolve over time, the term *initial rhythm* is somewhat of a misnomer, as it up until the connection of a defibrillator is unknown. For example, VF or VT, if left untreated, will gradually progress to asystole with a concurrent decrease in survival rates – although the exact time course seems to vary.[19,20] Conversely, PEA and asystole can transform into shockable rhythms, which has been reported to be

negatively associated with outcome in some cohorts,[14,21] but the other way around in different study populations.[22] A meta-analysis has suggested that this discrepancy might be explained by differences between PEA and asystole, where conversion from asystole to a shockable rhythm was positively associated with outcome, while conversion of PEA to a shockable rhythm showed a negative association.[23]

4.1.2.3 In-hospital and out-of-hospital cardiac arrest

In-hospital cardiac arrest (IHCA) differs from out-of-hospital cardiac arrest (OHCA) in several key areas, leading to them being classified as separate entities. Where EMS response times and bystander capabilities are important prognostic factors in OHCA, outcome after IHCA is more dependent on recognition and treatment of underlying causes.[24]

The spectrum of aetiologies also tends to be wider in IHCA, with some cases being caused by new cardiac events and other the result of a deterioration in the condition for which the patient is hospitalised.[25]

This thesis focuses solely on out-of-hospital cardiac arrest.

4.1.2.4 Outcome

For a condition inevitably leading to death if left untreated, mortality might intuitively seem like the best outcome measure. Although often used due to its robustness, it has to remembered that the leading cause of death among patients admitted to intensive care after OHCA is withdrawal of life supporting therapies (WLST) due to severe hypoxic-ischemic brain injury with perceived poor recovery potential.[26] Survival rates are thus affected by the threshold for WLST, with low rates of WLST potentially leading to an increased proportion of survivors in a persistent vegetative state. Measures of neurological function are therefore a more meaningful outcome, and should be reported whenever possible.[3]

Neurological function after cardiac arrest is generally reported using one of two classification methods: The modified Rankin scale (mRS)[27] or the cerebral performance category (CPC),[28] with the former being the preferred choice by the International Liaison Committee on Resuscitation (ILCOR).[29] These scales measure similar functional domains, but their categories are not directly comparable. They are, however, commonly dichotomised into what is considered *good* and *poor* outcomes as presented in table 1.

Table 1. Neurological outcome classficiation.

Dichotomised outcome	Modified Ranknin scale	Cerebral Performance Category
Good	0. No symptoms at all. 1. No significant disability. Able to carry out all usual activities, despite some symptoms. 2. Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities. 3. Moderate disability. Requires some help, but able to walk unassisted.	CPC1. Good cerebral performance: Conscious, alert, able to work and lead a normal life. May have minor psychologic or neurologic deficits. CPC2. Moderate cerebral disability: Conscious. Sufficient cerebral function for part-time work in sheltered environment or independent activities of daily life.
Poor	4. Moderately severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted. 5. Severe disability. Requires constant nursing care and attention, bedridden, incontinent. 6. Dead.	CPC3. Severe cerebral disability: Conscious. Dependent on others for daily support due to impaired cerebral function. Ranges from patients who are ambulatory but have severe memory disturbances or dementia precluding independent existence, to those who are paralyzed and can communicate only with their eyes, as in the “locked in” syndrome. CPC4. Coma or vegetative state: Unconscious. Unaware of surroundings, no cognition. No verbal and/or psychologic interaction with environment. CPC5. Brain death.

4.1.3 Epidemiology of out-of-hospital cardiac arrest

The overall incidence of OHCA is close to 50 cases per 100 000 population and year in multiple reports from Europe, the United States, Australia and New Zealand[30–34] but with substantial variation between subpopulations.[32,33] The reported incidence in 27 national European OHCA registries during October 2014 is presented in figure 2.

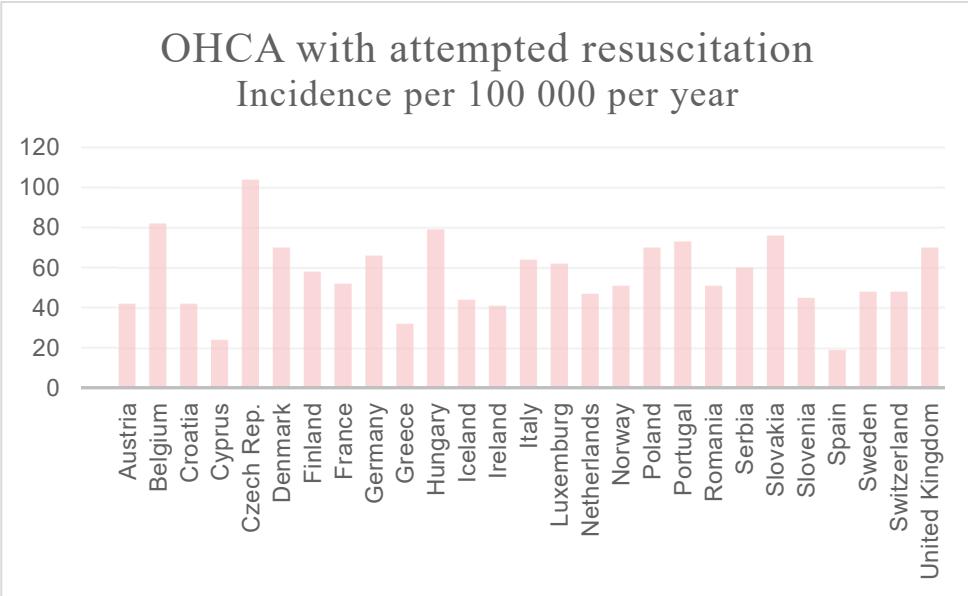

Figure 2. Extrapolated incidence from EuReCa ONE - a one-month analysis of 27 European OHCA-registries in October 2014. Adapted from Gräsner et al 2016.[32]

About two thirds of the patients are male and the presumed cause of arrest is per the latest *Utstein*-template[3] classified as *medical* in more than 90 % of all cases.[12,33] Most events occur at home, and asystole is the overall most common initial rhythm, albeit with great variation between registries.[33,35] In Sweden, approximately 5500 to 6000 cases of OHCA with attempted resuscitation have been reported to the SCRR each year for the last five years.[36] For 2020, this equates to an incidence of 57 per 100 000 inhabitants per year.

The proportion of patients alive 30 days after OHCA in the Swedish Cardiopulmonary Resuscitation Registry has been relatively stable around 11 % since 2010.[36] This is higher than the global and European average, both estimated in large analyses of multiple registries to be around 8 % at hospital discharge.[32,33,37,38] These averages must, however, be interpreted with caution due to substantial heterogeneity with survival rates ranging from less than 5 % for some registries to more than 20 % in others.[32,33,37]

This highlights a general issue regarding comparison of outcomes after OHCA. With outcomes generally expressed as the proportion of patients with good outcome divided by all patients with attempted resuscitation, a lower threshold to initiate resuscitation efforts will inevitably decrease the proportion of patients with good outcomes by increasing the denominator.

The so-called *Utstein-comparator* has been proposed as a means to better enable direct comparisons between different EMS-systems.[3] By including only patients with an undisputable indication for initiation of CPR and a high likelihood of a cardiac cause (bystander witnessed, shockable cardiac arrest), treatment effects on survival are maximised while selection bias is kept to a minimum. Even in this highly selected group, however, a recent pan-European study found great inter-registry variability with reported survival rates ranging from 0 to more than 50 % (figure 3), indicating that there is more to the international variation than the threshold to initiate resuscitation.[33]

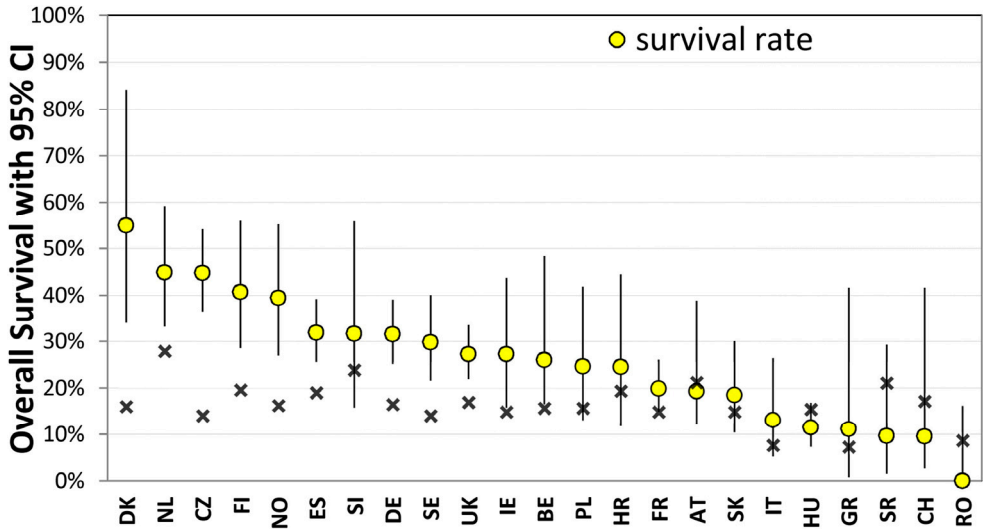

Figure 3. Overall survival in Utstein comparator group of the EuReCA TWO study.[33] Bars indicate 95% confidence interval. X indicates prevalence of Utstein comparator status among all patients with started resuscitation. Countries with <10 cases were excluded. Copyright Elsevier. Reproduced with permission.

4.2 Cardiopulmonary resuscitation

4.2.1 History

Although cardiac arrest physiologically is the cessation of cardiac mechanical activity, the arguably most distinguishing feature from other causes of unresponsiveness is absent or abnormal breathing caused by insufficient oxygen supply to the brainstem. Due to this, or perhaps a lack of understanding of the circulatory system, early resuscitation efforts tended to focus primarily on restoring ventilation. While Galen already 177 AD for demonstrative purposes showed that the lungs of a dead animal could be inflated using bellows,[39] it took another 1600

years until methods of manual artificial ventilation saw practical use as a resuscitative measure.[40] The effectiveness of these early negative-pressure methods was doubtful, however, and the modern era of simple airway manoeuvres and positive-pressure ventilation was pioneered by Peter Safar through his hallmark experiments on curarised volunteers in the 1950s.[41]

The potential of resuscitation methods aiming to restore circulation was not realised until Shiff's 1874 discovery that manual compressions of a canine heart in an open thorax seemed to yield carotid pulsations.[42] The transition of cardiac massage into clinical practice might have been accelerated by chloroform anaesthesia becoming increasingly popular despite anaesthesia-induced cardiac arrest being recognised as a potential complication.[43,44] This method of restoring circulation was, however, by its nature confined to the operating theatre and closed chest compressions did not gain widespread acceptance until proven effective by Kouwenhoven et al. in 1960.[45]

This marked a turning point in resuscitation history. The work of Safar, Kouwenhoven and their colleagues meant that their new concept of *cardiopulmonary resuscitation* could move outside the operating theatre to be much more than a last resort of treating anaesthetic or surgical complications. Through considerable educational efforts by Safar and colleagues, *CPR* quickly gained traction within both the medical and general community, for the first time providing a therapeutic option for out-of-hospital cardiac arrest,[46] finally giving meaning to the distinction between cardiac arrest and sudden death.

4.2.2 The chain of survival

The arguably most revolutionary aspect of CPR was the appreciation that neither closed chest compressions, nor mouth-to-mouth breathing could restore normal physiology when performed alone, but that the combination of the two into one concept could be successful. Further recognising that resuscitation depends on a series of actions performed with minimal delay, the American Heart Association adopted the so called *chain of survival* in 1991, stressing that no chain is stronger than its weakest link.[47] It has since evolved into being a core part of international CPR guidelines and educational material, with slight adaptions between different resuscitation organisations.

Figure 4. The European Resuscitation Council chain of survival.[48] Copyright Elsevier, reproduced with permission.

4.2.2.1 Early recognition and call for help

The first link is early recognition – not only of cardiac arrest, but also of warning signs that might precede many cases of cardiac arrest.[49] Prompt activation of emergency medical services might then prevent cardiac arrest altogether, or at least provide optimal conditions for the links that follow.

4.2.2.2 Early CPR

Cardiopulmonary resuscitation seldom leads to ROSC in itself, but it effectively buys time for causative therapies. Analyses of large registries indicate that immediate initiation of bystander CPR upon recognition of cardiac arrest doubles or triples chances of survival.[50–52] Reliance on EMS to start CPR is not feasible, as their arrival in most cases will be too late. This point is unfortunately further emphasised by the steadily increasing EMS response times in Sweden.[53]

4.2.2.3 Early defibrillation

Although not addressing the cause of malignant arrythmias directly, defibrillation is the by far most effective causative therapy in cardiac arrest able to rapidly restore a perfusing rhythm. Its effectiveness, however, is time dependent with chances of survival declining by approximately 5-10 % for every minute delay to defibrillation in shockable rhythms.[50,51,54] It is thus reasonable to assume that measures to increase timely access to defibrillators can increase survival among patients with shockable rhythms. Public access defibrillation programmes promoting and facilitating timely use of automated external defibrillators (AEDs) are therefore encouraged in guidelines, despite a lack of direct evidence.[1]

4.2.2.4 Early advanced care

Prior to the 1990s, intensive care after OHCA had received relatively little attention from the scientific community – possibly reflecting a view at the time that the 'damage had been done' and little could be done to change that after initial resuscitation. Compiling data from mainly experimental studies, however, Negovsky and Gurvich proposed the existence of a whole-body reperfusion syndrome they called the *post-resuscitation syndrome* in 1995, in which oxidative stress might cause additional brain injury.[55] After two hallmark trials indicating improved outcomes for patients treated with mild induced hypothermia after OHCA in the early 2000s[56,57] induced hypothermia gained traction as a treatment of the *post cardiac arrest syndrome*.[58] The beneficial effects of induced hypothermia could, however, not be reproduced in a series of larger randomised trials,[59–61] possibly indicating that the therapeutic effects seen in early trials could be attributable to avoidance of post-resuscitation fever.[62] Regardless of target temperature, the importance of high-quality intensive care with simultaneous diagnosis and treatment of underlying causes of arrest as well as functional assessments to support survivors in their recovery are emphasised in current guidelines.[63]

4.2.3 Advanced and basic life support

Like *cardiopulmonary resuscitation* combined two techniques into one easy-to-learn concept, resuscitation organisations provide therapeutic guidelines combining the elements of the *chain of survival* into resuscitation algorithms, commonly adapted to the educational level of the intended provider. The ERC calls these *basic life support* (BLS)[1] and *advanced life support (ALS)*[64]*,* respectively. Both include the core elements of the *chain of survival*, but the ALS-algorithm includes additional elements such as intravenous access and drug administration (figure 5). Beyond the treatment algorithm itself, the ALS concept also highlights the importance of considering and treating potential reversible causes of cardiac arrest using the 4H/4T-mnemonic (figure 5).

The additional elements of the ALS algorithm have not been shown to increase survival to hospital discharge when added to a well-functioning EMS system,[65] and in other instances, the effects of the algorithm are hard to separate from those of the higher educational level of ALS providers.[66] The overall level of evidence supporting the use of adrenaline and anti-arrythmics management in cardiac arrest is, however, low.[67–69]

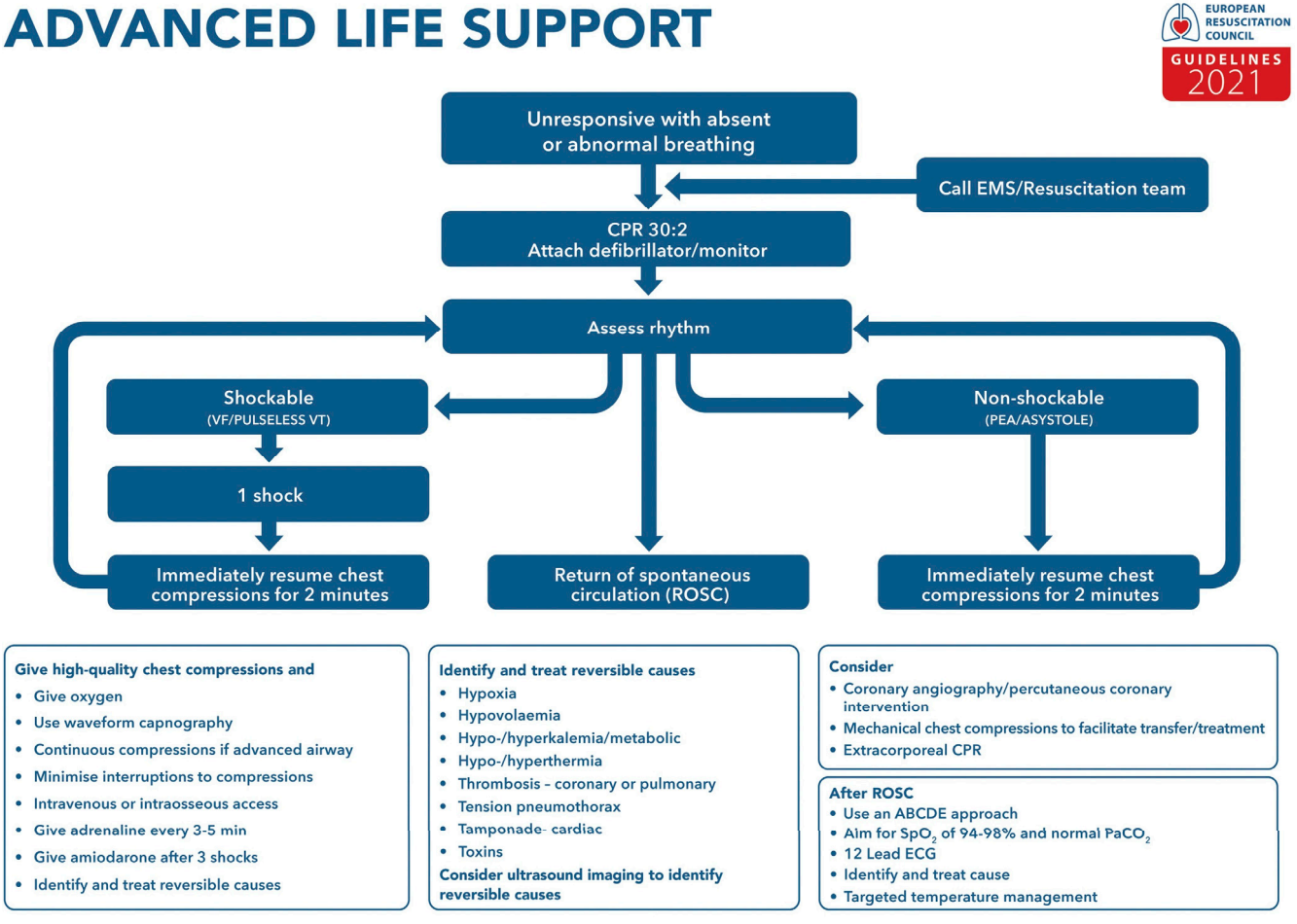

Figure 5. Adult advanced life support algorithm.[64] Copyright Elsevier. Reproduced with permission.

4.3 Automated chest compression devices

4.3.1 Physiology of chest compressions

That chest compressions are effective in producing forward blood flow in cardiac arrest is well-established, but the underlying mechanism is still, more than 60 years after Kouwenhoven's rediscovery of closed chest compressions in 1960,[45] debated. Kouwenhoven himself proposed the *cardiac pump* theory, where the heart itself acts as a pump through direct compression of the ventricles between the sternum and the thoracic spine. This concept has, however, been challenged by observations that forceful variations in intrathoracic pressure without any direct manipulation of the heart (i.e. coughing) still might produce sufficient forward blood flow to maintain consciousness after the occurrence of malignant arrythmias, popularly called *cough CPR*.[70] Although *cough CPR* cannot be recommended as a primary resuscitative measure,[71,72] these observations have led to the formation of the so called *thoracic pump* theory. In this model, the sudden rise of intrathoracic pressure created by chest compressions induces blood flow from the entire intrathoracic vasculature to the lower pressure compartments of the rest of the body. Retrograde flow is thought to be prevented by pressure-induced collapse of systemic veins at the thoracic inlet in combination with closure of venous valves.[73]

Theoretically, either of these theories could be confirmed or refuted by examining the blood flow through the mitral valve during chest compressions. If systemic blood flow in CPR is mediated through the *cardiac pump* phenomenon, the mitral valve should close during compression of the ventricles and open on decompression, whereas the *thoracic pump* theory postulates it should remain open during the entire compression-decompression cycle (figure 6). The advent of transoesophageal echocardiography has made such assessments possible, but available studies show a heterogenous pattern where the mitral valve appears to close on the downstroke of chest compressions in some, but not all patients – indicating that none of the theories alone are enough to explain all mechanisms in play.[74–76]

Several later variations of these hypotheses have been proposed,[75,77,78] but like their predecessors, they all share the common feature that they are hard to prove. Thus, the definitive answer to this question likely will remain to be elucidated until clear clinical implications are seen.

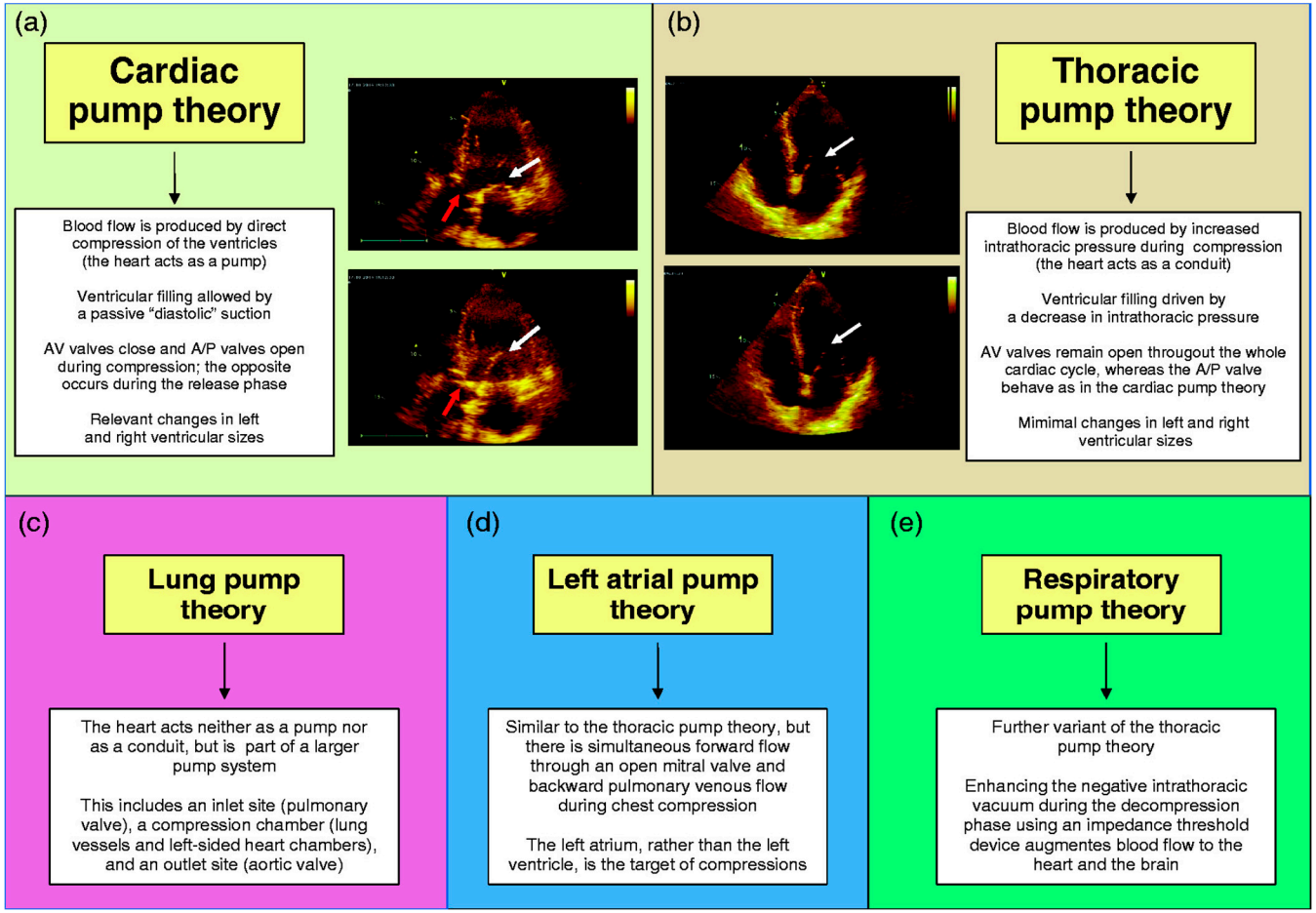

Figure 6. Chest compression blood flow theories. Adapted from Cipani et al. JICS 2019.[79] Copyright SAGE, reproduced with permission.

4.3.2 Evolution of mechanical chest compression devices

Based on the concepts outlined in the previous section, many attempts have been made to perfect closed chest compressions. Adjuncts designed for this purpose can be either manual or automated, with inventive solutions found in both categories. With manual devices having the same limitations as conventional, manual chest compressions when it comes to transporting patients with ongoing CPR, automated chest compression devices will be the focus of this thesis.

Early automated devices replicated manual chest compressions using a pneumatic piston or electric motor, but were hampered by their large size, making clinical use impractical or outright impossible.[80,81] The first device to be systematically evaluated in a clinical setting was the *Thumper* (Michigan Instruments, MI, USA), a somewhat portable gas-powered piston compressor that was found to yield similar outcomes to manual CPR in an in-hospital setting.[82] In a way, the neutral results could be expected, as these devices simply replicated Kouwenhoven's concept of closed chest compressions, adding only automaticity and consistency.

More novel methods started to emerge when attempts to exploit the *lung pump* hypothesis gained traction through Halperin's work with circumferential chest compressions – nicknamed *vest CPR* from the vest-like appearance of the device.[83] Around the same time, methods to enhance the pressure difference between the up- and downstroke components of the compression cycle begun to be developed. The manual active compression-decompression device *CardioPump*, remembered by many due to its close resemblance to a toilet plunger, showed promising clinical results[84] while Steen and colleagues adapted the technology into their automated *LUCAS* (Lund University Cardiac Assist System).[85]

Both the *LUCAS* and Halperin's vest have since been developed into commercial products, the *LUCAS®* (Jolife AB, Lund, Sweden / Stryker Medical, MI, USA) and the *AutoPulse®* (ZOLL Medical, Chelmsford, MA, USA). These are the to date only two automated mechanical chest compression devices to be extensively tested in large, randomised clinical trials.

4.3.3 LUCAS®

The LUCAS® is a piston-based, automated active compression-decompression device. While early models were pneumatic, using medical gas supplies to power its piston, later iterations are battery powered. Multiple reports have indicated improved haemodynamics with LUCAS-CPR over manual CPR,[85,86] but this has not translated into improved outcomes in randomised controlled trials enrolling more than 7000 patients.[87–89]

Early reports of a more severe injury pattern seen in autopsies of non-survivors treated with this device raised safety concerns,[90] and a stabilising strap was introduced by the manufacturer to prevent caudal migration of the device during operation.[91] From observational studies it is clear that severe injuries can occur during LUCAS-CPR,[92–94] but lack of methodological standardisation make comparisons difficult. A study of a convenience sample of patients from the randomised LINC-trial indicated a significantly higher frequency of rib fractures in patients and a higher crude incidence of some soft tissue injuries treated with the LUCAS® device,[95] whereas LUCAS-CPR was found to be noninferior to manual CPR in a randomised safety trial evaluating serious or life-threatening injuries.[96]

4.3.4 AutoPulse®

An evolution of Halperin's *vest CPR*, the AutoPulse® uses an electric motor attached to a rigid backboard to repeatedly tighten and loosen a load-distributing band around the patient's thorax, thereby inducing circumferential chest compressions. Like the LUCAS®, the AutoPulse® has been associated with enhanced hemodynamics over manual CPR[97] but not improved clinical outcomes.[98,99] The ASPIRE-trial – the first large-scale, randomised controlled trial on automated mechanical chest compressions for OHCA – was even terminated early due to poor outcomes in the intervention group.[98] Nevertheless, a later reanalysis indicated that a protocol change at a single site likely was to blame, with the remaining sites showing results more favourable for the AutoPulse® at the point of trial termination.[100] The follow-up CIRC-trial, with a strict protocol and high levels of monitoring, confirmed equality of AutoPulse-assisted CPR with high-quality manual CPR.[99]

It has been hypothesized that use of AutoPulse® might result in less traumatic injuries than traditional sternal chest compressions due to its force being applied through a larger contact area.[97] Post-mortem findings, however, indicate that the use of this device might be associated with a slightly different but nonetheless serious injury pattern dominated by an increased frequency of posterior rib fractures and pneumothorax/pneumomediastinum.[96,101–103] As a result, AutoPulse® did not meet the noninferiority margin of the only randomised safety study of the device to date.[96]

The exact mechanisms of these injuries are not known, but the AutoPulse® is significantly more powerful than the LUCAS® according to a ZOLL technical report.[104] One might also speculate that the application of force across the entire anterior portion of the thorax as opposed to just the sternum could increase strain on the posterior section of the ribs, as less motion will be exerted through the more flexible costochondral joints.

4.4 Transport with ongoing CPR

There are only two possible immediate outcomes of attempted resuscitation in out-of-hospital cardiac arrest: Return of spontaneous circulation or death following termination of resuscitation.

Unfortunately, an EMS crew does not have the luxury to simply choose the former, but rather faces a critical question when spontaneous circulation does not return after a period of their maximal efforts on scene – should we take the patient to hospital, or is it time to terminate resuscitation?

This is a topic of contention,[105] and current practice standards are highly divergent between EMS systems (figure 7),[32] indicating that this is a question unlikely to have a universally correct answer.

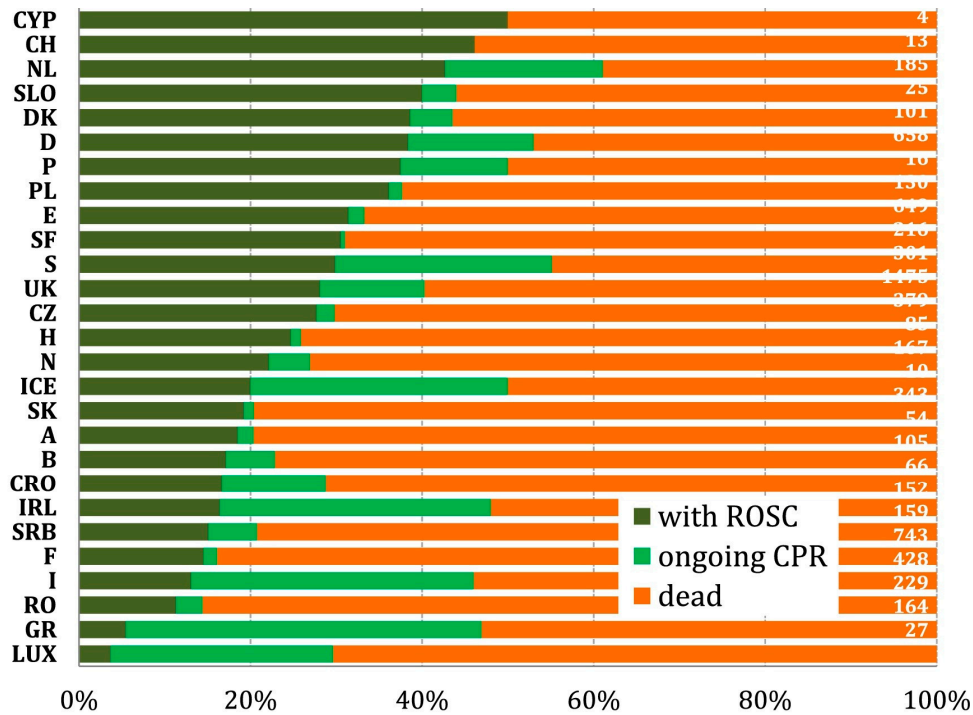

Figure 7. Status on hospital admission for 6884 OHCA patients included in the EuReCa ONE-study. Patients included in the 'Dead' category either died at scene or were pronounced dead on arrival at hospital. Numbers to the right of each bar represent the total number of cases per country. Country codes are available in the original publication. Reproduced from Gräsner et al.[32] under the CC BY NC ND-license.

4.4.1 Legislative and cultural aspects

As outlined above, transport with ongoing CPR is intrinsically linked to termination of resuscitation. Where field termination of resuscitation is not accepted for legal or cultural reasons, transport with ongoing CPR will be norm rather than an actively chosen treatment option. This is the case in Japan and most other east Asian countries, [106,107] whereas prehospital termination of resuscitation generally is legally allowed in the Europe and the USA. Local protocols might, however, stipulate more or less rigorous criteria depending on the educational level of prehospital providers.

Both the American Heart Association and European Resuscitation Council provide guidelines for termination of resuscitation,[108,109] yet their implementation into clinical practice is variable.[110,111] Qualitative studies have identified several potential reasons for this, including a "rescue culture" among EMS providers possibly fuelled by public expectations and discomfort with death disclosure.[112] Experiences from Denmark, where prehospital physician services are a long-standing tradition, indicate that physician presence can significantly decrease futile transports with ongoing CPR without compromising overall outcomes.[113,114]

4.4.2 Practical aspects

Transporting patients with ongoing resuscitation efforts is not practical. Traveling in road ambulances is bumpy,[115] access to the patient severely restricted and some procedures, like manual chest compressions, put providers at risk for death or serious injury by requiring them to work unrestrained.[116] The patient is also put at risk; just during extrication from a victim's house lengthy CPR pauses of up to 10 minutes have been reported[117] and conflicting reports suggest that transportation in some cases might be associated with lower CPR quality in some settings.[118,119] Automated chest compression devices have been shown to improve some of these aspects[117,120] and importantly increases safety for providers by allowing them to be work restrained.

Despite these constraints, peri-arrest transportation might somewhat counter-intuitively be the least resource-intensive solution for the EMS. When resuscitation efforts are terminated in the field, the prehospital providers themselves are responsible for consoling relatives, helping them make arrangements with a funeral home after first having got hold of a physician or medical examiner to complete the declaration of death.[112] Cardiac arrests in public locations are especially problematic in this aspect, and were a common reason for non-compliance in an implementation trial of a termination of resuscitation-rule.[111]

4.4.3 Ethical and family aspects

Relatives and family members are also stakeholders in this dilemma. While EMS providers might feel pressured to do *everything* in the presence of family members, there is some data to suggest that prehospital termination of resuscitation generally is well accepted by most relatives and preferred by some.[121,122] Transporting patients to hospital will also result in the separation of the patient from his or her family at least temporarily, going against ample evidence indicating that family presence during resuscitation efforts might help in the recovery process after failure of such attempts by reducing anxiety and feelings of regret.[123,124] A recent survivor- and family led scoping review of family needs when experiencing cardiac arrest identified that most published reports indicate that survival of the family-member naturally is and should be the key priority, but also that unnecessary resuscitation is experienced as brutality and dehumanisation.[125] Extending futile resuscitation attempts by taking the patient to hospital therefore does by no means eliminate the ethical challenges of termination of resuscitation.

4.4.4 Current guidelines

Based on the evidence outlined above, current European guidelines do not recommend routine transportation to hospital for any patient category, but highlights that systems should implement criteria for early transport to hospital for patients deemed likely to benefit from such treatment in that particular system – taking local factors into account.[109] Termination of resuscitation rules are supported as an objective aid to guide clinical decisions, but the need to consider the outcome of any such rule only as one part of a holistic patient assessment is stressed.[109]

4.5 In-hospital interventions

From a patient perspective, it probably does not matter whether resuscitation is performed next to or inside an ambulance. What the destination has to offer in terms of additional, potentially life-saving treatment is likely more interesting than the transport there.

4.5.1 Percutaneous coronary intervention

Immediate coronary angiography with subsequent percutaneous coronary intervention (PCI) targeting coronary occlusions or stenoses is the well-established gold standard for treatment of acute ST-elevation myocardial infarction (STEMI), and this extends also to patients presenting in cardiac arrest with ST-elevations on the post-ROSC 12-lead ECG.[126]

The diagnostic sensitivity of the post-resuscitation 12-lead ECG has, however been challenged by multiple angiographic studies identifying coronary occlusions in a significant proportion of patients without evidence of ST-elevations.[127–130] This has raised the question of whether all patients resuscitated after OHCA in whom no obvious non-cardiac cause of arrest is identified should be taken for an early coronary angiography. Three recent randomised trials including more than 1000 patients resuscitated after OHCA without signs of ST-elevation on their 12-lead ECG have, however, not shown improved short-term survival with such a strategy.[131–133]

It has also been suggested that coronary angiography can be performed during CPR using automated chest compression devices in patients where the suspicion of a coronary event causing the arrest. This has been shown to be feasible for patients taken to the cardiac catheterisation laboratory with spontaneous circulation, but reports of outcomes for patients arriving with ongoing CPR are scarce with conflicting results.[134,135] It is also unclear whether novel invasive circulatory support devices such as the *Impella®* (Abiomed, MA, USA) might have role to increase feasibility of the latter,[136,137] or if peri-arrest PCI should be reserved for patients receiving extracorporeal CPR (eCPR).

4.5.2 Extracorporeal resuscitation

Extracorporeal resuscitation or eCPR refers to the practice of using a rapidly deployed, peripherally cannulated veno-arterial extracorporeal membrane oxygenator (ECMO) for patients in cardiac arrest, thereby providing sufficient flow of oxygenated blood to maintain homeostasis in critical organs while the root cause of arrest is treated.[138] Although far from new, the evidence supporting this highly invasive therapy is weak, with just two randomised trials to date evaluating its performance either alone[139] or as part of a "hyperinvasive" bundle of therapies.[140] These trials largely confirm the results from observational studies in that eCPR is feasible in certain settings and could be beneficial for selected patients.[141–143]

Identifying those select patients is, however, as challenging as crucial for this extremely resource intensive intervention to be implemented in clinical practice. Current guidelines from the Extracorporeal Life Support Organisation (ELSO) do not endorse any specific set of selection criteria due to a lack of evidence, but offer several suggestions to be considered in a local context (table 2).[138]

Table 2. Suggested inclusion criteria for eCPR.[138] Copyright Extracorporeal Life Support Organization. Reproduced with permission.

Example of Inclusion Criteria for ECPR
Age < 70 years[144]
Witnessed arrest
Arrest to first CPR ("no-flow interval") < 5 minutes (*i.e.*, bystander CPR)
Initial cardiac rhythm of VF/pVT/PEA
Arrest to ECMO flow < 60 minutes "low flow interval"*
ETCO2 > 10 mm Hg (1.3 kPa) during CCPR before cannulation for ECMO
Intermittent ROSC or recurrent VF
"Signs of life" during conventional CPR may be a positive predictive factor for survival
The absence of previously known life limiting comorbidities (*e.g.* end stage heart failure/chronic obstructive pulmonary disease/end-stage renal failure/liver failure/terminal illness) and consistent with patient's goals of care
No known aortic valve incompetence (>mild aortic valve incompetence should be excluded)
*Unless other favorable prognostic features are present: *e.g.*, periods of intermittent ROSC/hypothermia prearrest/young age/signs of life during CPR. CPR, cardiopulmonary resuscitation; ECMO, extracorporeal membrane oxygenation; ECPR, extracorporeal cardiopulmonary resuscitation; ROSC, return of spontaneous circulation.

4.5.3 Other interventions

A minority of patients with OHCA might benefit from other interventions targeting specific reversible causes of arrest (see section 4.2.3 advanced life support). Most of these interventions have not been specifically studied in the setting of cardiac arrest but are extrapolated from emergency medical guidelines and will not be covered in detail in this thesis.

Severe accidental hypothermia leading to cardiac arrest is, however, an exception where the poor evidence basis for eCPR outlined in the previous section does not apply. Systematic reviews have suggested survival rates of more than 70 % for witnessed cases of primary hypothermic arrest rewarmed using ECMO[145] and more than 20 % even for unwitnessed cases.[146] Due to the diminished oxygen demand associated with lower body temperature in vertebrates,[147] good outcomes are possible even after extended periods of CPR and current guidelines recommend extracorporeal rewarming if available within 6 hours.[148]

4.6 Risk prediction in out-of-hospital cardiac arrest

4.6.1 Prediction of futility during resuscitation

Many clinical decision rules (CDR) have been proposed to help identify patients where continued resuscitation efforts can be considered futile.[149–153] These are commonly called termination of resuscitation (TOR) rules.

The challenges of creating such rules are multiple: They can only rely on factors which are obvious to the EMS crew in the emergency setting, they must be simple enough to be reliably interpreted while performing CPR and they should only identify patients who, had resuscitation been continued, would not have survived with an acceptable neurological outcome.

While there are some fairly straight-forward ways to fulfil the first two of these prerequisites, the latter constitutes an ethical challenge. It has been proposed that all TOR rules should be designed to predict death or poor neurological outcome to aid comparability.[154] The ideal tool would correctly differentiate all patients destined to die (100 % sensitivity) from all survivors (100 % specificity, 0 % false-positive rate), but no such diagnostic test exists in the world of medicine. When designing a CDR for termination of resuscitation, the most important ethical implication is to not falsely induce termination of resuscitation in patients who would have survived. This makes *specificity* (i.e. the tool's ability to identify survivors) the most important diagnostic measure together with its inverse concept *false positive rate* (i.e. the number of survivors falsely predicted to die divided by all patients predicted to die). To maximise the specificity (and thereby minimising the FPR), a trade-off can be made where lower *sensitivity* (i.e. the ability of the tool to correctly identify patients who will die), is accepted as the consequences associated with unnecessary transports to hospital are greatly outweighed by those of missing survivors.

Prior to adoption of any CDR into clinical practice, it must be validated in datasets unrelated to that in which the tool was developed. Upon successful external validation, it is shown that the predictive abilities seen in the development cohort were not caused by spurious correlations in that particular dataset, and that the tool works as intended also for the population making up the validation cohort.[155]

The most rigorously validated tools to date are those developed by Morrison et al, of which the BLS-TOR,[150] later proposed to be the *universal* TOR (uTOR),[156] stands out with external validations performed in Canadian,[157,158] Korean,[159] and American[156,160] cohorts. It has also been validated clinically through an implementation trial.[111] A recent ILCOR *Consensus on Science with Treatment Recommendations* (CoSTR) systematic review found no suitable studies to include in a meta-analysis on the topic of prehospital termination of resuscitation rules and

classified the overall certainty of evidence as very low.[161] Crude diagnostic properties of the uTOR in external validation cohorts are presented in table 3.

Table 3. Diagnostic properties of the uTOR for predicting death in external validation cohorts. Grunau et al. 2017 evaluated application of the uTOR at different timepoints. Adapted from ILCOR CoSTR: Prehospital termination of resuscitation (TOR) rules

	Specificity (%, 95 % CI)	Sensitivity(%, 95 % CI)
Morrison et al. 2009[156]	100 (97 - 100)	57 (55 - 60)
Drennan et al. 2014[157]	89 (83 - 94)	43 (42 - 45)
Grunau et al. 2017 at 6 min[158]	91 (89 - 93)	72 (71 - 73)
Grunau et al. 2017 at 30 min[158]	100 (100 - 100)	46 (45 - 47)
Jordan et al. 2017[160]	100 (83 - 100)	24 (16 - 34)
Yoon et al. 2019[159]	81 (77 - 84)	70 (69 - 72)

From these data, it is evident that the diagnostic performance of the uTOR, while overall high, is variable with both time of application[158] and study setting, which is further highlighted in a systematic review and meta-analysis including more than 200 000 patients evaluated with the BLS- or uTOR.[162]

4.6.2 Risk prediction after successful resuscitation

Less than 50 % of patients admitted to intensive care after successful initial resuscitation from OHCA survive to hospital discharge, with a clear majority of survivors having a good neurological outcome.[60,163] For patients who expire in hospital, the leading cause of death is withdrawal of life supporting therapies (WLST) due to severe brain injury with perceived poor recovery potential.[26] In these cases, the decision to WLST should be and typically is informed by a delayed, multimodal neuroprognostication performed at least 72 hours after cardiac arrest as advocated by international guidelines.[63]

There is, however, a group of patients who die early due to either cardiovascular causes or multiorgan failure,[26] where urgent escalations of care might come into question to prevent imminent death. With the invasiveness of such escalations increasing as the field of mechanical circulatory support advances, there is also an increased need for objective early estimates of a patient's risk of severe brain injury to avoid subjecting patients to unwarranted and potentially harmful therapies. As a potential solution, a multitude of prediction models to estimate a patient's risk of a poor outcome after OHCA have been developed.[164] Most of these *risk scores* were designed to work in the early phases after cardiac arrest, i.e. in the emergency department or upon admission to the intensive care unit (ICU) and thus utilise prognostic factors readily available in this setting.

In terms of external validity, two scores stand out with both having been validated in multiple populations:[164] The Cardiac Arrest Hospital Prognosis (CAHP)[15] score with a median area under the receiver operating characteristics curve (AUROC) in seven external validation cohorts of 0.85 (range 0.75 – 0.91) for predicting binary neurological outcome[164,165] and the Out-of-Hospital Cardiac Arrest (OHCA)-score[166] with a median AUROC in ten external validation cohorts of 0.80 (range 0.57 – 0.88) for predicting binary neurological outcome.[164,165] Both these scores are based on multivariable logistic regression models, but whereas the OHCA-score is calculated manually using only slightly modified parameters from the regression model, the CAHP-score is estimated using a nomogram. Neither of these scores can therefore be estimated without the use of external aids.

Two newer alternatives with lower mathematical demands on their end-user are the Targeted Temperature Management-score[13] (TTM) and the MIRACLE$_2$-score,[14] which both are estimated using only basic summation of their respective score items. The TTM-score was developed within the first TTM-trial[59] and is used to predict binary neurological outcome from ten different prognostic factors. The MIRACLE$_2$-score was developed using a dedicated single-centre registry and predicts binary neurological outcome using seven prognostic factors. External validation in two different cohorts yielded AUROC 0.91 and 0.84, respectively,[14] with the TTM-score achieving similar results (AUROC 0.91) in its only external validation to date.[165]

4.6.3 Ethical aspects of attempting to predict futility

The works of Schneiderman and colleagues are frequently quoted when medical futility is discussed, often only highlighting his quantitative description of "a common-sense definition of futility" that was "if a treatment has not worked in the last 100 cases, almost certainly it is not going to work if it is tried again".[167,168] Translated into statistical terms, this would mean that a CDR designed to predict death or poor neurological outcome would be acceptable to use if it was at least 99 % specific – i.e. misclassified 1 in 100 patients. For most other clinical tests, this would be regarded as extremely accurate – yet, when asked, a majority of clinicians in an intensive care survey deemed they would need a test with tenfold higher specificity (i.e. 99.9 % or FPR 0.1 %) to comfortably recommend WLST.[169]

Unfortunately, it is extremely unlikely that a clinical test with an FPR truly less than 0.01 % will ever be discovered. There are of course many examples of trials where no false positives are identified and FPRs of 0 % therefore rightfully are reported, but as soon as the 95 % CI is considered, its upper boundary will almost inevitably surpass 0.1 %. And if it would not – would we then perhaps start advocating for reporting the 99 % CI instead?

Managing uncertainty is arguably the hardest part of medicine, but practitioners at all levels still do it every day. Very few decisions during a clinician's day are made

with a validated CDR and the FPR of a day's assessments is therefore largely never known. For that, most practitioners probably are thankful, as few would be below 0.1 %.

But the solution is not to avoid statistics and epidemiological data altogether. While uncertainty cannot be eliminated from medicine, its influence can be diminished. With more and better data supporting the critical decisions that must be made, outcomes might just improve for both patients and caregivers alike.

5 Aims of the thesis

The overall aims of this thesis are:

To describe current practice regarding mechanical chest compressions, transport with ongoing CPR and other interventions during and in the early phases after out-of-hospital cardiac arrest.

To identify readily available prognostic factors associated with death or poor neurological outcome after out-of-hospital cardiac arrest, which could be used to avoid exposing patients to futile therapies.

Specifically, the main objectives of each paper were:

I. To describe current practice regarding the use of automated chest compression devices in Sweden.

II. To report a Swedish single-centre experience regarding patients transported with ongoing resuscitation after OHCA and in-hospital interventions provided.

III. To report experiences regarding patients transported with ongoing resuscitation from three British hospitals and evaluate the universal termination of resuscitation rule in this population.

IV. To validate two novel risk prediction scores in unconscious patients admitted to intensive care after OHCA and compare their performance to two well-validated alternatives.

6 Materials and methods

This thesis includes four papers, the designs and populations of which are summarised in table 4. The data sources for papers I and IV (the SCRR and the TTM-2 trial, respectively) are presented in their own sections, whereas papers II and III are retrospective cohort studies where the majority of data was extracted from medical records. Below follows a narrative description of the most important methodological aspects of each paper, with details available in the attached papers.

Table 4. Methodological overview of papers I-IV.

Paper	I	II	III	IV
Design	Retrospective analysis of a national quality registry.	Retrospective single-centre cohort study.	Retrospective cohort study.	*Post-hoc* analysis of an international, multicenter, investigator-initiated trial.
Study population	Patients with attempted CPR after OHCA in Sweden between 2011 through 2015, with valid data on survival status and mode of CPR (automated or manual).	Patients transported to the emergency department of Skåne University Hospital, Lund, Sweden with ongoing CPR after OHCA between 2010 through 2015.	Patients transported to one of three hospitals in West Midlands, UK with ongoing CPR after OHCA between September 2016 and November 2017.	Unconcious patients admitted to intensive care following OHCA of presumed cardiac cause randomised to targeted temperature management at 33ºC or controlled normothermia between 2017-2020 with known neurological outcome at 6 months.
No. of patients	N = 24316	N = 409	N = 227	N = 1829

6.1 The Swedish Cardiopulmonary Resuscitation Registry

The SCRR, one of Sweden's more than 100 national quality registries, is a prospectively recorded, comprehensive source of Utstein-style patient and event characteristics in cardiac arrest. The original OHCA-only registry was founded in 1990 and in 2006, a separate IHCA-module was added. For the projects in the present thesis, only the OHCA-registry was used.

All patients with attempted CPR are included in the registry. Since 2010, cases are registered using a web-based electronic case report form (eCRF) directly by the EMS providers, whereas hospital-level and 30-day outcome data are added to the registry for all patients admitted to hospital by a local coordinator. Long-term patient reported outcome data (PROM) are collected via telephone interviews with survivors 3-6 months after cardiac arrest and are part of the registry since 2014. Survivors are informed of their participation in the registry and their right to have their records erased.

After a retrospective analysis of selected regions indicated that as many as 30% of OHCA cases might not have been reported to the registry up until 2010,[170] yearly regional audits in combination with measures to increase the quality and frequency of EMS reporting have since resulted in a current coverage estimated to be close to 100%.

6.2 The TTM-2 trial

The *Targeted Hypothermia versus Targeted Normothermia After Out-of-hospital Cardiac Arrest (TTM-2)* trial[60] compared the effects of a target temperature of 33ºC after OHCA with early treatment of fever, defined as a body temperature ≥37.8°C. The study protocol and protocol for outcome reporting and follow-up have been published separately.[171,172] The protocol was approved by the ethics committees in each participating country and informed consent was obtained from all patients who regained mental capacity.

This was an international, multicentre, randomised superiority trial with 61 sites from Europe, the United States, Australia, and New Zealand having included patients at the end of the trial. Patients were eligible for inclusion if they remained unconscious after successful resuscitation from OHCA of a suspected cardiac origin and the most important exclusion criterion was unwitnessed cardiac arrest with an initial rhythm of asystole.

A total of 1900 patients were included during a recruitment period of slightly more than 2 years (November 2017 – January 2020), which after losses gave an intention-to-treat population of 1861. The trial did not show a benefit for hypothermia with regards to its main outcome of survival status at 6 months (relative risk of death 1.04 [95 % CI 0.94 – 1.14]), nor were there any signals in either direction for the secondary outcome of neurological function at 6 months or in any of the prespecified subgroups.

Importantly, the TTM-2 trial protocol used strict criteria for WLST, which was not allowed due to a presumed poor neurological prognosis prior to 96 hours. Thereafter, WLST was allowed only for patients fulfilling the TTM-2 criteria for a likely poor neurological prognosis, summarised in figure 8. This minimises bias regarding the value of early prognostic markers.

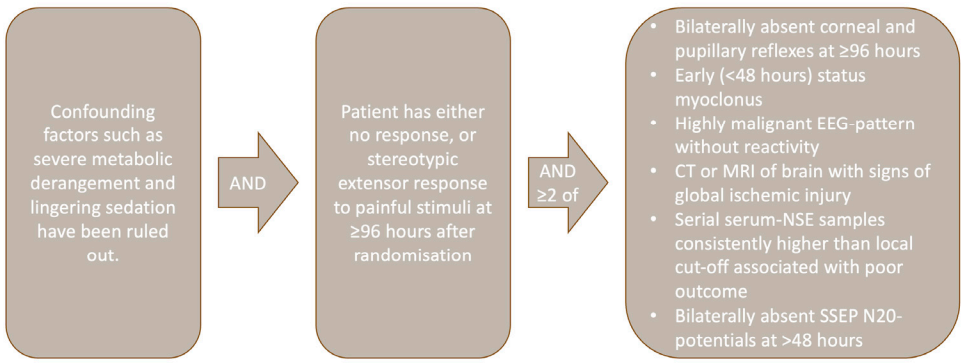

Figure 8. The TTM-2 criteria for a likely poor prognosis.[171] EEG: Electroencephalogram. CT: Computed tomography. MRI: Magnetic resonance imaging. NSE: Neuron-specific enolase. SSEP: Somatosensory evoked potentials.

6.3 Paper I

Paper I is a national overview of how automated chest compression device were used during attempted resuscitation of OHCA in Sweden between January 1st 2011 and December 31st 2015. Cases were identified using the SCRR, which is described in section 6.1. This study was approved by the local ethics committee of the university of Gothenburg.

The main objective of this registry study was to describe patients in whom an automated chest compression device was used during resuscitation and compare them to patients resuscitated by manual CPR alone. Although the risk of bias is high when studying the association between a therapeutic intervention and survival in an observational study such as this one, we elected to do so as a secondary outcome

while adjusting for available known confounders. The reason for this was that although randomised trials have not indicated an association between the use of automated chest compression devices and survival, their real-world implementation might introduce new factors of concern not present in the monitored setting of randomised trials. Lower levels of training and less experience with the device could for example lead to delays in device deployment and/or other therapies.

Baseline data were presented both on a nationwide level and across regions, which were grouped according to automated chest compression device use (low, intermediate, high). For the secondary outcome of the association between the use of automated chest compression devices and survival, two approaches were used:

1. *Propensity score matching*, where a logistic regression model is fitted to predict the probability of being treated with an automated chest compression device was fitted from a set of covariates hypothesized to be associated with both the exposure (use of an automated chest compression device) and outcome (i.e., a *confounders*). This probability, or *propensity score*, is estimated for all patients in the study population and then used to match patients who were treated with an automated chest compression device with patients who were not. Matching on similar propensity scores ensures that patients that the confounders used to estimate the propensity score are distributed equally across the group treated with an automated chest compression device and those who were not, thus balancing the groups and isolating the effect of automated chest compression devices. While very effective in creating balanced groups, this approach has the drawback that a substantial amount of information might be discarded due to missing data and insufficient overlap between the groups, potentially resulting in loss of power and limited generalisability.
2. *Multivariable logistic regression,* where missing data first are handled by *multiple imputation*. Here, an iterative algorithm uses patterns in observed data to generate multiple estimates to replace missing data. The iterative process retains variance and results in overall less bias than as opposed to *single imputation* methods. In this study, 50 imputed datasets were created in which a diagnostic multivariable model of survival in relation to ACC device use and the same covariates used in the propensity score approach described above, the results of which were pooled. Compared to the propensity score approach, this method is associated with a higher degree of uncertainty due to imputations and the general linearity assumption of regression analysis. On the other hand, it allows for inferences about subjects who were not matched in propensity score approach, increasing power and generalisability.

As none of the methods described is *a priori* superior to the other, results from both were reported. Due to the large sample size, even minute differences unlikely to be

of clinical importance would yield low p-values. We therefore 1) chose a significance level of $\alpha = 0.01$ and 2) report the standardised difference between survivors and non-survivors, which is not affected by sample size,[173] in addition to traditional inferential tests. For comparisons between the propensity score matched groups, tests suitable for paired data were used for covariates included in the propensity score.

6.4 Paper II

The clinical question which gave rise to paper II was:

> *"For patients transported to hospital with ongoing CPR, what is the outcome, and to what extent are the therapeutic options of the hospital utilised?"*

Patients arriving in to Skåne University Hospital in Lund, Sweden, after OHCA between January 2010 through December 2015 were identified using a local registry logging the responses of the in-hospital cardiac arrest team. The team responds to in-hospital emergencies around the clock and are routinely alerted when a patient with OHCA arrives, regardless of whether ROSC has been achieved. Patients in whom *sustained ROSC* was not achieved prior to hospital arrival were included in the final study population. The study was approved by the local ethics committee of Lund University and survivors were informed about the study in their right to opt out.

Skåne University Hospital, Lund, is a tertiary teaching and referral hospital with around-the-clock cardiac catheterisation availability but no eCPR protocol. Its primary catchment population is about 330 000 and the EMS system serving it has full ALS capabilities in all vehicles, each manned by a crew of two – of whom at least one is a registered nurse with specialist training. There was no physical prehospital physician service in place during the study period, but EMS crews had over-the-phone access to physician consult at all times. All vehicles carry an automated chest compression device (LUCAS®) and guidelines in place during the study period encouraged early transport to hospital regardless of whether ROSC had been achieved.

The registry logs basic patient characteristics and treatment data, but additional data were retrieved both from the SCRR and from medical records. The presence and location of any ROSC episodes and specific interventions were retrieved from medical records using a custom template based on the 4H/4T-mnemonic for reversible causes of cardiac arrest endorsed by resuscitation guidelines (see figure 5).[64] Interventions which neither were part of the ALS-algorithm, nor met the criteria of specific interventions against reversible causes of arrest outlined in table 5, were classified as *"supportive"* and noted as free text and reported as a *post-hoc*

classification. Reasoning that only interventions with the potential to help achieving sustained ROSC would justify transport with ongoing CPR from a patient perspective, interventions performed after sustained ROSC had been achieved were excluded.

The main outcome was survival to hospital discharge. As a secondary objective, the performance of the universal termination of resuscitation rule (uTOR) was evaluated using the diagnostic measures of *specificity* and *positive predictive value*.

*Table 5. Classification of interventions against reversible causes of arrest. *Due to a high frequency of crystalloid administration without any recorded indication, only transfusion of blood products was classified as a targeted intervention against hypovolemia.*

Reversible cause	Intervention
Hypoxia	Advanced airway manoeuvres
Hypovolemia	Blood transfusion*
Hypo-/hyperkalemia	Potassium correction
Hypothermia	Rewarming manoeuvres including ECMO
Thrombosis	Coronary angiography
	Intravenous thrombolysis
Tamponade	Pericardial decompression
Tension pneumothorax	Pleural decompression
Toxins	Administration of any antidote

6.5 Paper III

Paper III sought to investigate the same clinical question as paper II in a different medical system and a slightly different focus. While paper II is concentrated primarily on interventions and evaluates the uTOR only as a secondary outcome, paper III studied patient characteristics and therapies in relation to uTOR-classification and *special circumstances* defined below.

The study was performed in what was then the Heart of England National Health Service (NHS) Foundation Trust in West Midlands, UK, where patients arriving in the emergency department of one of its three acute hospitals after OHCA between September 2016 and November 2017 were eligible for inclusion. The study received institutional approval by the trust audit and effectiveness team as per local guidelines.

Heartlands Hospital, Good Hope Hospital and Solihull Hospital serve a population of 1.2 million in and around the city of Birmingham. They are all attended by the West Midlands ambulance service, which responds to cases of OHCA with BLS and ALS capable units staffed by a combination of paramedics and emergency medical technicians. Paramedics were allowed to withhold or terminate resuscitation efforts in cases fulfilling a fixed set of criteria (*recognition of life*

extinct – ROLE, table 6). A prehospital physician service was available around-the-clock, and its presence could be requested by the EMS crew or emergency dispatcher when needed.

Patients with OHCA were identified using a local registry of emergency department visits and were included in the final study population if screened medical records indicated they were transported with ongoing CPR. Patients in whom cardiac arrest was sustained under *special circumstances* as defined by the *ROLE*-criteria (e.g. drowning, hypothermia, pregnancy, poisoning or overdose) were grouped separately, whereas the remaining patients were classified according to the uTOR with outcomes reported separately for each of the three groups. Interventions prior to hospital arrival were extracted from ambulance records using an *Utstein*-template,[3] whereas all in-hospital diagnostic and therapeutic interventions during the current hospital stay, regardless of time from arrest in patients eventually admitted, were categorised separately. The main outcome was neurological outcome at hospital discharge.

Table 6. Recognition of life extinct (ROLE) criteria.

Joint Royal Colleges Ambulance Liaison Committee (JRCALC) recognition of life extinct (ROLE) criteria
Resuscitation may be withheld or terminated in/when:
Conditions unequivocally associated with death:
Massive cranial or cerebral injury
Hemicorporectomy
Massive truncal injury
Decomposition or putrefaction
Incineration
Hypostasis
Rigor mortis
Patient pulseless and apnoeic where one or more of the following facts are established:
Presence of DNAR / Validated Advanced Directive
Expected death as a result of a terminal illness (eg. ambulance transfer to hospice)
Asystole with no evidence of CPR in past 15 minutes and no signs of: • Drowning • Hypothermia • Poisoning or overdose • Pregnancy
Asystole and prolonged submersion (adults >1h, children >1.5h)
Following 20 minutes of advanced life support (ALS) where all of the following are confirmed: • No palpable pulses • No heart sounds • No respiratory sounds • Pupils fixed and dilated • Asystole on ECG for 30 seconds

6.6 Paper IV

In paper IV, the aim was to compare two established and well-validated risk prediction scores for patients successfully resuscitated from OHCA (the OHCA- and CAHP-scores,[15,166] respectively) to two newer and slightly less complex alternatives (the TTM- and MIRACLE$_2$-scores).[13,14] The population in which we sought to perform this four-way comparative validation study was that of the TTM-2 trial,[60] which has been described in a previous section. As all the evaluated scores are designed to predict neurological outcome, only patients with data on neurological outcome at 6 months after cardiac arrest available were included (n = 1829, 98.3 % of the entire intention-to-treat population of 1861). The primary outcome was poor neurological outcome at 6 months, in the TTM-2 trial defined as mRS 4-6 (moderately severe disability, severe disability and death). The mRS is described in more detail in section 4.1.2.4 *Outcome* and *table 1*.

All score items and their distribution across the different scores are presented in figure 9, and a detailed overview of each score is available in figure 10. Due to missing data in a few predictors, multiple imputations by chained equations were used to generate 50 imputed datasets, from which the final results were either pooled or reported as minimum and maximum values across all imputations.

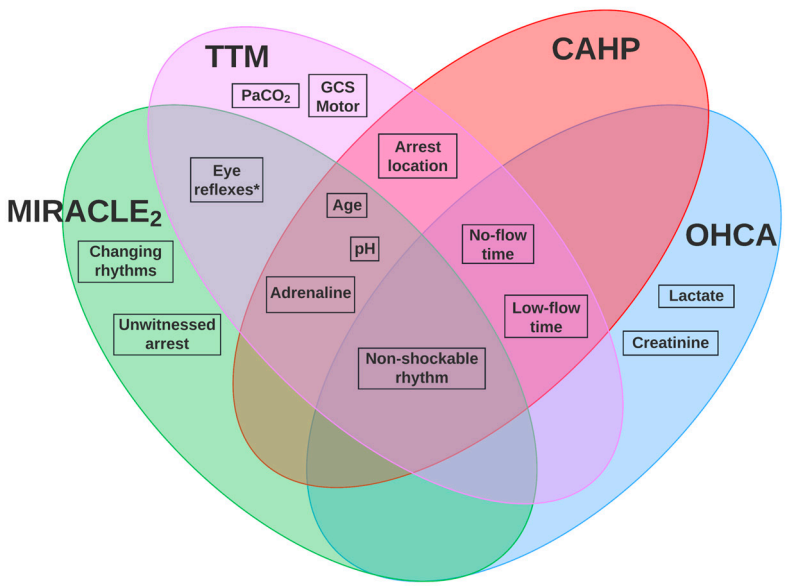

Figure 9. Venn-diagram of score items.

All four scoring systems were originally derived using predictive multivariable logistic regression modelling and should therefore ideally be validated in accordance with the *Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD)*-statement.[155] To assess a prediction model, a number of measures must be considered:

- The model's *discriminatory* performance, i.e., its ability to correctly classify patients to a binary outcome across a range of input values. This is commonly presented as a *receiver operating characteristics* (ROC)-curve, the area under which (area under the curve, AUC or *C-statistic*) corresponds to the discriminatory performance of the model. A ROC-curve can assume any shape between a straight diagonal line from corner to corner (corresponding to the discriminatory performance of a coin toss or an AUC of 0.5) and a perfect square (corresponding to perfect discrimination or an AUC of 1.0). There is no uniformly accepted classification of AUC values, but values >0.8 are generally considered good to excellent in clinical medicine.
- The model's *calibration*, i.e. the agreement between the predicted and observed outcomes has been called *the Achilles heel of predictive analytics* due to its tendency to be overlooked.[174] It can be assessed in a number of ways, such as by comparing the overall event rate to the predicted event rate (*calibration-in-the-large*) and plotting the observed versus predicted event rate, where predictions ideally should correspond to what is observed. A poorly calibrated model might still have adequate overall discriminatory performance as assessed by the AUROC, but its predictions for individual patients will be inaccurate.

In this study, however, we evaluated the scoring systems themselves (as depicted in figure 10) and did not have access to the full regression models (which have not been published in full for any of the evaluated scoring systems). This is representative for how the scoring systems would be used in clinical practice, but also means that the predicted risk estimates could not be determined. We therefore assessed calibration indirectly by plotting the rate of a poor neurological outcome over a range of score levels, whereas overall discriminatory performance was estimated more traditionally using ROC-curves.

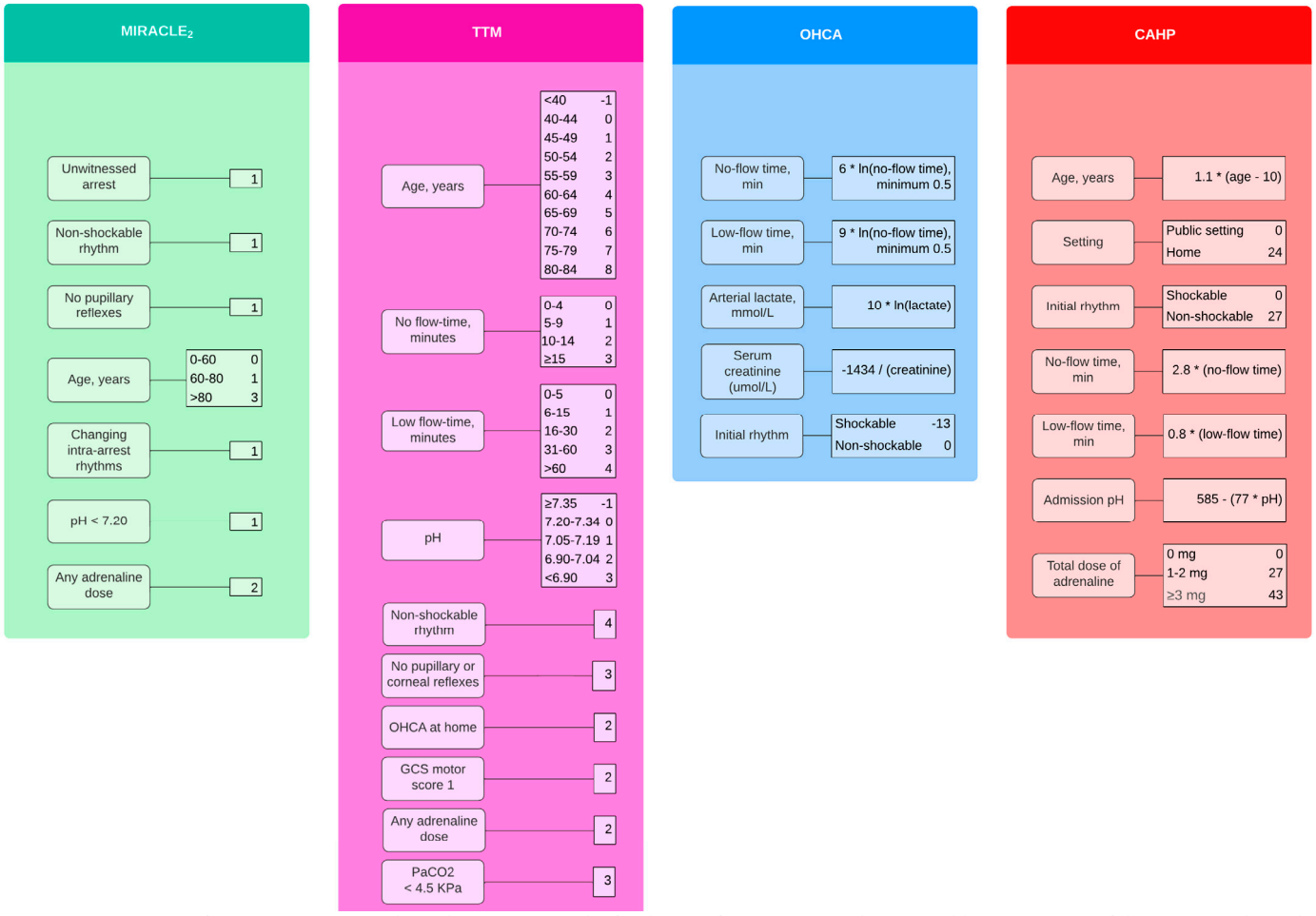

Figure 10. Overview of scoring systems evaluated in paper IV. The final score for a patient is determined by summation of the points in the right column of each score.

7 Results

Detailed descriptions of the results are available in each of the separate papers – see attachments. Below is a summary of the most important results of each paper.

7.1 Paper I

A total of 24316 patients were included in the final study population. Of these, 32.4% were treated with an ACC device.

7.1.1 Factors associated with the use of an automated chest compression device

The factors that showed the strongest associations with ACC device use in the unadjusted population were the year of cardiac arrest (increasing), treatment with adrenaline, a higher number of defibrillations and longer delays to the first defibrillation. Cases of OHCA where an ACC device was used were also less likely to be witnessed by the EMS crew, but the association between ACC device use and a longer delay to the first defibrillation remained with EMS witnessed cases excluded. The EMS response time was however slightly longer for ACC-CPR treated patients in this subgroup analysis.

7.1.2 Regional variation

The proportion of patients treated with an ACC device during the study period ranged from 79.8% of all OHCA in the county of Halland to 0.8% in the county of Södermanland (figure 11a). The 30-day survival rate ranged from 6.8% in Västernorrland to 14.6% in Jämtland (figure 11b). When regions were grouped according to degree of ACC device utilisation (<10 %, 10-50 % and >50 %), a trend towards lower survival rates with increasing ACC-device use was seen (11 to 10 %, $p_{trend} = 0.008$).

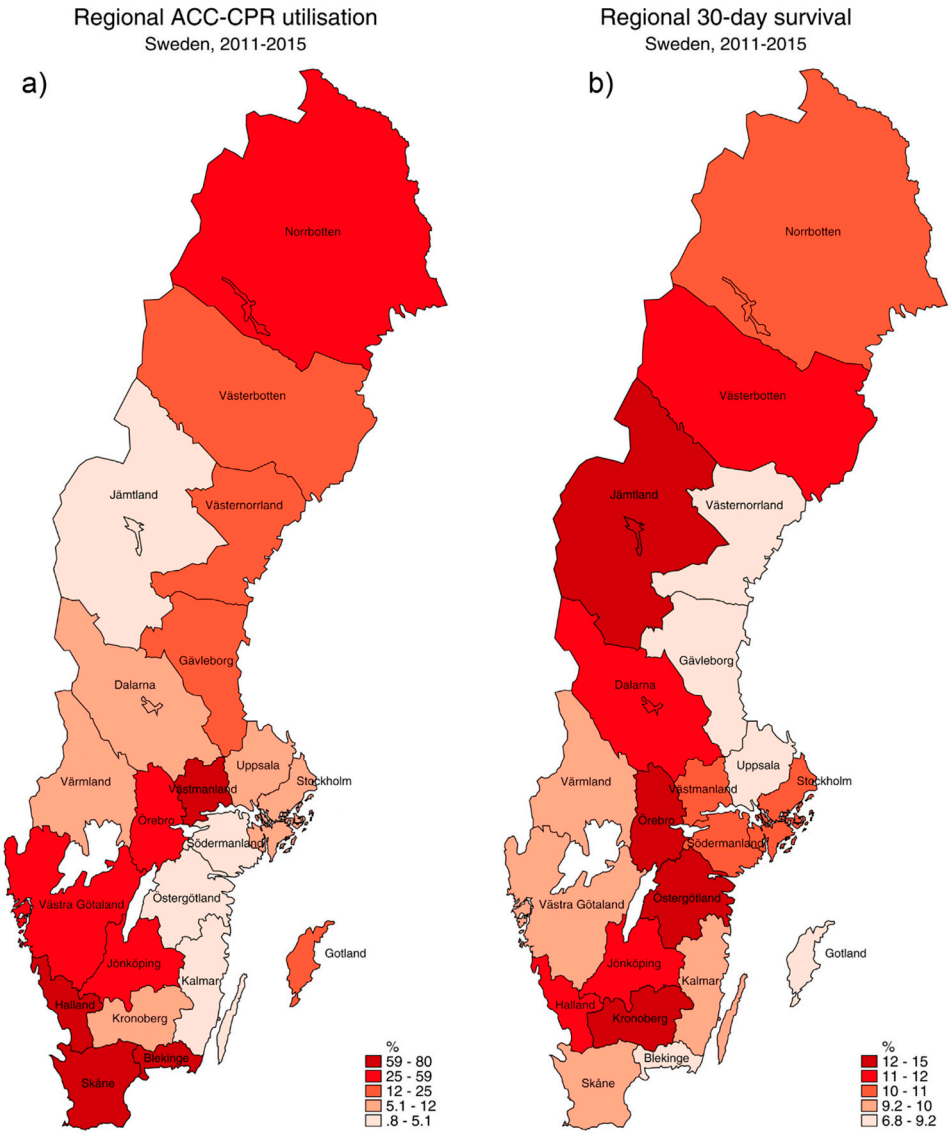

Figure 11. Regional variation in survival and use of automated chest compression devices in Sweden 2011-2015.

7.1.3 Association between automated chest compression device use and survival

Crude, unadjusted 30-day survival was 6.3 % for patients treated with an ACC device, compared to 12.8 % for patients receiving manual CPR only. To account for confounding, a propensity score was estimated, as outlined in the methods sections, using the following variables: Year of cardiac arrest, age >70 years, sex, initial rhythm, witness status, location of arrest, presumed cardiac aetiology, adrenaline treatment, intubation, anti-arrhythmics, delay from emergency call to EMS arrival >15 min as well as interactions of all these with adrenaline treatment. Matching 1:1 on the propensity score was successful for 13922 patients (57.3% of the full study population), generating two well-balanced groups. The overall survival in the matched cohort was 7.0 %; 6.2 % for patients treated with an ACC device and 7.9 % for patients receiving manual CPR only ($p < 0.001$).

Using logistic regression in conjunction with multiple imputation in the full study population ($n = 24316$) to adjust for confounding (using the same variables as for the propensity score) and account for missing data, as described in the methods section, the negative association between ACC device use and 30-day survival remained (odds ratio 0.62 [95% CI 0.54 - 0.71], $p < 0.001$). When also adjusting for region of arrest, the odds ratio was 0.58 (95% CI 0.50 - 0.68, $p < 0.001$).

7.2 Paper II

A total of 409 patients arriving in the emergency department 2010 through 2015 without having achieved sustained ROSC in the prehospital setting were identified from the cardiac arrest team registry. In-hospital sustained ROSC was eventually achieved in 13 % of these patients, and 1.7 % survived to hospital discharge (figure 12).

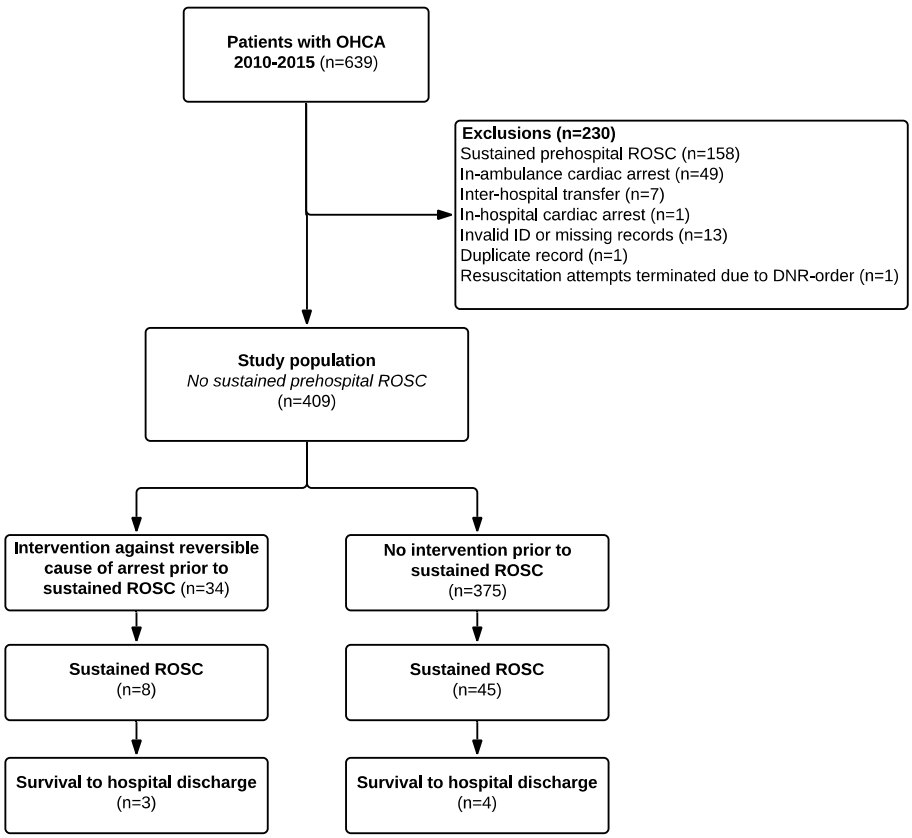

Figure 12. Flowchart of patients in paper II.

7.2.1 In-hospital interventions prior to sustained ROSC

Any therapy outside the ALS algorithm was given to 21 % of all patients, but only a minority of these were classified directly targeting a potentially reversible cause of cardiac arrest (occurring in 8 % of all patients). Such specific interventions are presented in table 7.

Table 7. Specific interventions against potentially reversible causes of cardiac arrest. One patient might have received more than one intervention. Therapies might in some cases have been initiated during a period of non-sustained ROSC.

Intervention	No. of attempts	No. of attempts followed by sustained ROSC	No. of attempts followed by survival to hospital discharge
Advanced airway manoeuvres	7	3	1
Blood transfusion	1	0	0
Potassium correction	1	0	0
Rewarming after hypothermia	1	0	0
Coronary angiography	7	3	2
Percutaneous coronary intervention	5	2	1
Pericardial decompression	9	1	0
Intravenous thrombolysis	4	1	0
Pleural decompression	1	0	0
Antidote administration	5	0	0
Unique patients	**34**	**8**	**3**

7.2.2 The universal termination of resuscitation-rule (uTOR)

All factors needed to determine uTOR-status were known for 91 % of all patients. The uTOR would have recommended termination of resuscitation in 30 % of the entire study population, including 2 of the 7 patients who eventually survived to hospital discharge. The corresponding specificity was 71 % and the positive predictive value 98.4 % (95 % CI 94.9 - 99.5 %). Sensitivity analyses indicated that missing data did not have the potential to substantially impact these results.

7.3 Paper III

Paper III identified a total of 227 patients arriving to one of the three study hospitals between September 2016 and November 2017 with ongoing resuscitation efforts after OHCA. Special circumstances as defined by *JRCALC ROLE*-criteria were present in 3 % cases. A total 7 % of all patients were eventually admitted and the overall survival rate to hospital discharge with a good neurological outcome (CPC 1-2) was 1.3 %. No survivors with poor neurological outcome (CPC 3-4) were identified.

7.3.1 The universal termination of resuscitation-rule (uTOR)

The uTOR criteria for termination of resuscitation were met in 39 % of all cases, including those with *special circumstances* (figure 13). No patient classified as such survived to hospital discharge, yielding a specificity of 100 % and a positive predictive value of 100% (95% CI 97.6–100.0%).

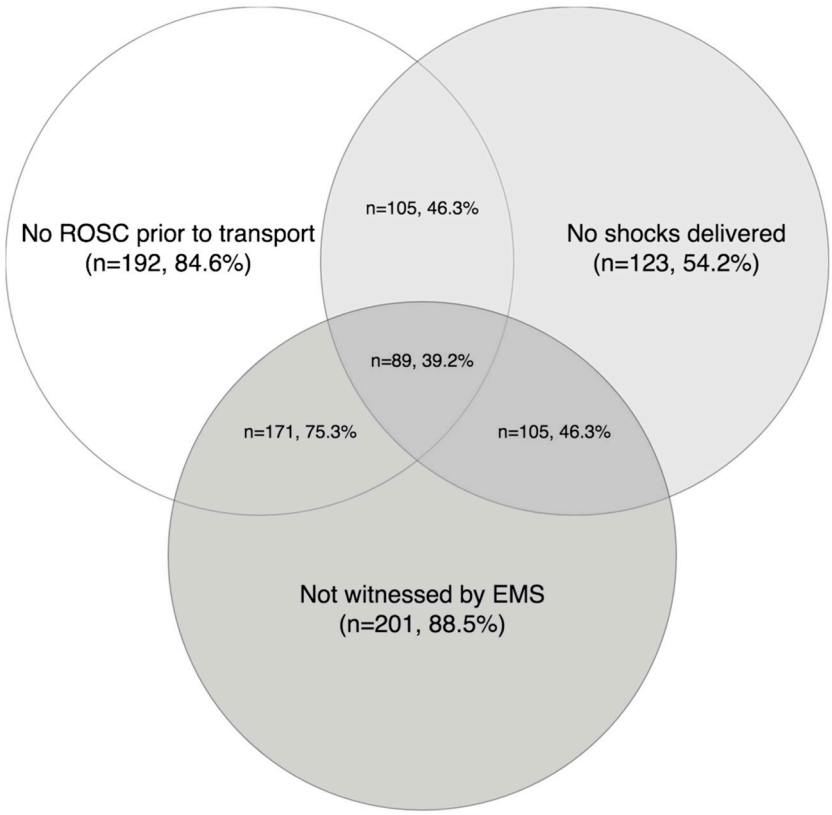

Figure 13. Venn diagram of uTOR criteria in paper III.

7.3.2 Patient characteristics

Patients with *special circumstances* (suspected overdose and pregnancy) were substantially younger than the rest of the cohort and by definition less likely to have a medical cause of arrest. Other baseline variables not included in the uTOR showed no substantial differences between the *uTOR = terminate* and *non-uTOR-terminate* groups. Within the *uTOR = terminate* group, the initial rhythm was split roughly equally between PEA and asystole.

7.3.3 Interventions

No major differences between groups were identified regarding prehospital interventions except for amiodarone administration and defibrillation as result of the uTOR filtering on shockable rhythms. Adrenaline was almost universally administered (99 % of all patients) and the airway was controlled with either a supraglottic device or by endotracheal intubation in more than 90 % of cases. An automated chest compression devices was used only in a single patient prior to hospital arrival (< 1 %).

After hospital arrival, patients in the *non-uTOR-terminate* group received a greater number of diagnostic and therapeutic interventions during the course of their hospital stay, with *advanced airway manoeuvres*, *echocardiogram* and medications not available in the ambulance service (*non-JRCALC-drugs*) being the most prevalent.

7.4 Paper IV

Of the 1861 patients included in the intention-to-treat population of the TTM-2 trial, 1829 had data on functional outcome at 6 months after cardiac arrest and were included in the study population of paper IV. The main outcome (death or poor functional outcome, defined as mRS 4-6) occurred in 54.0 % of all patients.

7.4.1 Individual predictors

Significant, unadjusted associations with the primary outcome were found for all individual predictors (see figures 9 and 10) included in the evaluated scoring systems except for unwitnessed arrest (part of the MIRACLE$_2$-score) and $PaCO_2$ <4.5 KPa (part of the TTM-score).

7.4.2 Discriminatory performance of the CAHP-, MIRACLE$_2$-, OHCA- and TTM-scores

Figure 14 shows ROC-curves for all evaluated scoring systems with the outcome being functional neurological outcome at 6 months after cardiac arrest. For each score, one thin line per imputation is drawn for a total of 50 lines per scoring system. The perceived line thickness in the figure thus represents the between-imputations variance. As evident from the pooled AUROC-estimates, all scoring systems were closely matched in terms of discriminatory performance, with the only the OHCA-score trailing slightly.

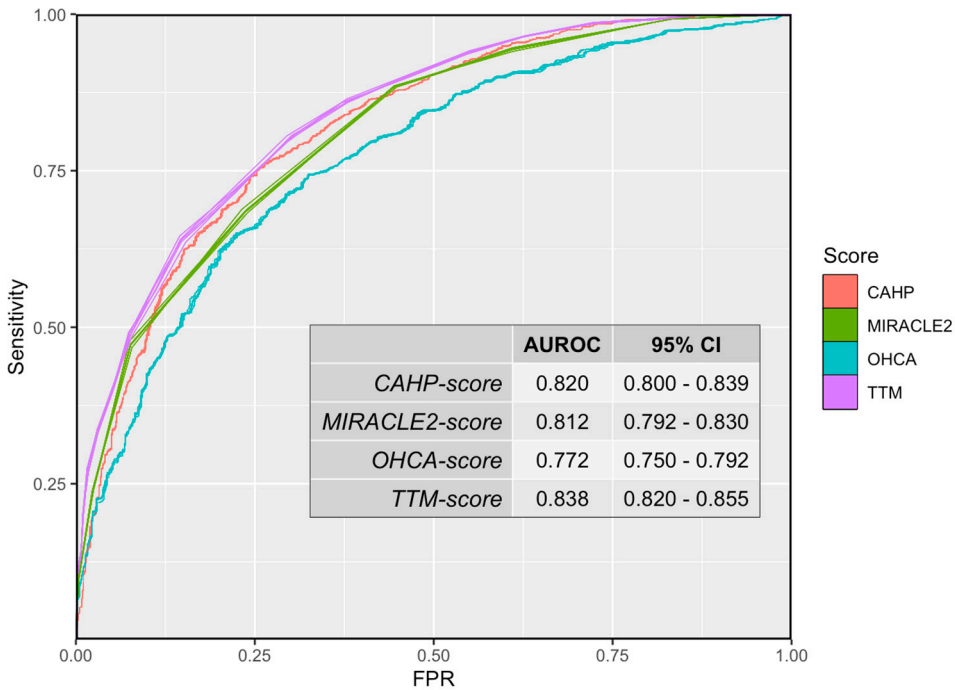

Figure 14. Receiver-operating characteristics curves (ROC) for all scoring systems evaluated in paper IV. One line per imputation (n = 50) per score. The area under the ROC-curve (AUROC) estimates are pooled from all imputations. FPR: False-positive rate (= 1 – specificity).

7.4.3 Observed outcome in relation to score levels

Figure 15 presents the calculated score of individual patients in relation to the observed outcome using data from the first imputed dataset. The continuous CAHP- and OHCA-scores have been categorised using equal-width binning with numbers on X-axis denoting the midpoint of each bin. The boundaries of the first and last bins (marked as "<" and ">") are open to negative and positive infinity, respectively. As evident from the relatively constant increase in poor outcome with each incremental increase in score levels, the relationship between score and outcome is roughly linear. The minimum score needed to achieve 100 % specificity in this population is roughly the first bar to reach 100 %, but other levels of specificity cannot intuitively be derived from this graphic.

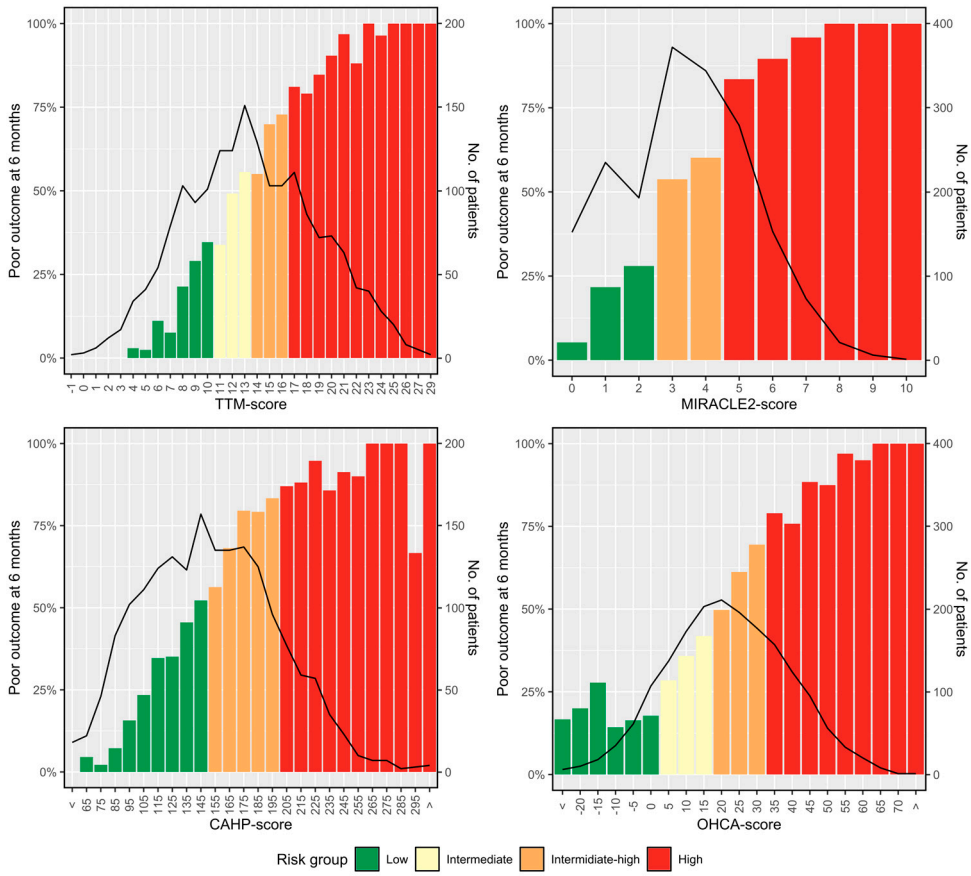

Figure 15. Score of individual patients in relation to observed outcome. Data from first imputed dataset only. Risk groups are classified according to the definitions in the original publication of each scoring system. Black line shows number of patients per bar (right Y-axis).

Mathematically derived from all 50 imputed datasets, the lowest cut-off possible to achieve >95 % specificity in this population was: >18 or >19 (minimum-maximum value between imputations) for the TTM-score, >5 for the MIRACLE$_2$-score, >38.2 for the OHCA-score and >191 for the CAHP-score.

8 Discussion

When introducing new therapies, a logical sequence of steps is to first identify a problem and then to develop measures to solve it. The development of automated chest compression devices started out like this – people die from cardiac arrest due to a lack of sufficient flow of oxygenated blood, and automated chest compression devices were developed to improve this critical component of CPR. Their usefulness in facilitating transportation of patients with ongoing resuscitation was, however, quickly identified by early adopters and resulted in a solution to an ill-defined problem – *why* would we want to transport patients with ongoing CPR?

This problem is of course not unique to automated chest compression devices and transporting patients with ongoing resuscitation has been done long before the advent of such devices; yet these devices and modern invasive methods for mechanical circulatory support inevitably create incentives for doing so to an increased extent.

The results of the works included in this thesis might help to better define this problem and offers insights into criteria to predict futility.

8.1 Automated chest compression devices

In paper I we show that the use of automated chest compression devices varies substantially between Swedish regions and that survival for patients treated with such devices was poor.

Multiple baseline imbalances between the two treatment groups favoured patients who received manual CPR only. This was also the case in several other non-randomised trials of automated chest compression devices[175–177] and most likely reflects selection bias where patients with favourable circumstances achieve ROSC before deployment of an automated chest compression device.

In the adjusted analyses of paper I, these baseline imbalances were neutralised. Yet, automated chest compression devices remained significantly associated with mortality. This finding is in conflict with those of all but one randomised trials on the subject,[87–89,99] raising the possibility of unmeasured confounding. There are indeed important factors not available in the SCRR which could be associated with

both survival and the efficacy of automated chest compressions, of which time of device deployment arguably is the most important. The adjusted analyses did account for markers of prolonged resuscitation attempts such as drug administration and endotracheal intubation, but without knowing the time of device deployment, it is possible that patients with high survival rates due to rapid ROSC were disproportionally represented in the manual CPR group even in our matched analysis.

It must, however, be acknowledged that the training level and familiarity of EMS personnel with the device in question also might affect outcomes. In paper I, the time to first defibrillation was longer among patients treated with an automated chest compression device, and this finding remained both in subgroup analyses excluding EMS-witnessed cases and in our matched analysis. As ROSC prior to a first defibrillation would be very unlikely, our main unmeasured confounder of ACC device deployment time should not apply here, and this finding could thus indicate that device deployment might delay defibrillation in some cases. This did not seem to be the case in randomised trials where the level of training and monitoring was reported to be high.[87,99] In the PARAMEDIC-trial, however, where the automated chest compression device was introduced into clinical practice as would any other new device,[89] significantly lower survival rates for patients in the LUCAS-arm were observed in the prespecified intention-to-treat subgroup analysis of patients with an initial shockable rhythm – possibly supporting this hypothesis.

In conclusion, all observational studies on automated chest compression devices have high risk for bias, and while sophisticated methods to adjust for confounding, such as propensity score matching, exist, they can only adjust for factors that are measured. With unknown factors being exactly unknown, matching methods might give the impression that a sample is more balanced than it really is, and must therefore be interpreted with caution. These facts notwithstanding, it must be acknowledged that a device proven to work in multiple randomised trials still can have negative clinical implications if implemented without due care.

8.2 Outcomes in patients transported with ongoing CPR

The overall survival rate for patients transported to hospital with ongoing resuscitation efforts was 1.7 % in paper II and 1.3 % in paper III. This is somewhat lower than data from Ontario, Canada (2.3 %, transport rate 54 % including patients with prehospital ROSC),[157] a large North American registry (3.8 %, transport rate 49 %)[178], Amsterdam, the Netherlands (4.4 %, transport rate 56 %)[179] and in stark contrast to Copenhagen, Denmark (20 %, transport rate 35 %).[114] In both paper II and III we used hospital-based registries and are therefore unable to definitely determine transport rates due to an unknown number of cases where resuscitation

efforts were terminated in the prehospital setting. With both the region of Skåne and West Midlands well covered by the SCRR and OHCAO[180]-registries, respectively, we were, however able to roughly estimate typical transport rates in the regions closest resembling the catchment area of the study hospitals. For paper II, this estimate is 60 % and for paper III slightly less than 50 %. Taking this into account, only the results from Copenhagen[114] are strikingly different to ours. As touched on in a previous section of this thesis, Denmark has a long-standing tradition of a prehospital physician service and all decisions to transport a patient with ongoing resuscitation efforts are made by prehospital physicians.[114]

In studies derived from OHCA registries reporting the total number of arrests with field termination of CPR[114,157,179] the survival rate for all patients without prehospital ROSC can be estimated by dividing the number of survivors in patients transported with ongoing CPR by the number transported plus all cases with field termination of resuscitation. This equates to remarkably similar survival rate for patients without prehospital ROSC of 0.9 % in the Ontario-study,[157] 0.8 % in the Copenhagen-study[114] and 1.2 % in the Amsterdam-study (albeit with some exclusions possibly affecting the accuracy of this estimate).[179] Extrapolating from our estimated transport rates, the corresponding figure would be 0.8 % for the population of paper II and 0.5 % for the population of paper III. Although these figures are nothing but rough extrapolations which should be interpreted as such, the more restrictive approach seen in the Copenhagen-cohort does not seem be necessarily associated with a loss of life.

8.3 In-hospital interventions

From papers II and III it is evident that patients arriving in the hospital with ongoing CPR seldom are recipients of life-saving interventions in settings where eCPR is not available. In paper II, where we specifically studied interventions performed during ongoing CPR (or prior to sustained ROSC in patients with periods of non-sustained ROSC) targeting potentially reversible causes of arrest, less than 1 % of all patients survived after having received a specific intervention, and all of these patients had evidence of non-sustained ROSC episodes prior to receiving the intervention.

Importantly, in paper III, both patients receiving an in-hospital intervention and patients who eventually survived to hospital discharge (regardless of having received an intervention or not) had significantly shorter prehospital durations of resuscitation than patients who did not receive an intervention or died. Other studies have indicated that, in patients transported with ongoing CPR, earlier decisions to do so might be associated with increased survival.[179,181] Like our study, these observational studies have a high risk of bias due to the potential of unmeasured factors influencing the decision of early transport. These studies also did not report

in-hospital interventions and it can therefore not be determined whether such therapies might have contributed to the higher survival rates seen in patients transported early.

Nevertheless, if a patient is transported with ongoing CPR due to a suspected reversible cause of arrest, the decision to do so should intuitively be made as early as possible. In paper III, the median duration of resuscitation prior to hospital arrival was 44 minutes, which might have both affected the threshold of clinicians to perform interventions at all and the outcome of the interventions actually attempted.

In this context, our results suggest that the benefits of in-hospital therapeutic options are limited in settings with high rates of transport with ongoing CPR. Further research is, however, needed to elucidate whether rapidly transporting select patients with ongoing CPR specifically for interventions such as eCPR might be feasible in a wider clinical context.

8.4 The universal termination of resuscitation rule

The uTOR was evaluated in papers II and III, where it would have prevented transportation of 30 % and 37 % of the respective study populations at the cost of two false positives in paper II. Both of these survivors presented with PEA, and while clinical information was unavailable for one, the other had a short duration of prehospital resuscitation and was found to have ROSC immediately on arrival to hospital. This highlights a general point of concern with the uTOR: Its specificity depends on time of application, with earlier application associated with higher false-positive rates.[158]

No patient with an initial rhythm of asystole survived to hospital discharge in either of the two study populations. The uTOR was originally developed as the BLS-TOR,[150] and therefore uses only a binary rhythm classification compatible with automated external defibrillators (AEDs). For ALS providers confident in manual rhythm analysis, differentiating PEA from asystole might add more prognostic information with PEA being potentially associated with better outcomes than asystole.[18,182]

8.5 Early risk scores

The main finding of paper IV is that all risk scores showed equally good to excellent discriminatory performance regarding a poor functional outcome at 6 months with no clinically relevant differences identified between scores, possibly barring the

OHCA-score which had a marginally lower AUROC and yielded slightly skewed risk estimates in its lower end.

As outlined in the methods section, calibration of the scores could not be assessed due to the lack of uniformly reported predicted outcomes for different levels of the score. With all original publications reporting diagnostic measures across different risk groups of their development cohorts, [13–15,166] comparisons of these with those of the present study can serve as a surrogate measure of calibration. Complete diagnostic data across the different risk groups defined by each score are available in table 3 of the attached paper IV.

The estimates of OHCA-score and to some extent also the CAHP-score in this study tended to overestimate the risk of a poor outcome compared to their development studies, evident by higher levels of specificity with correspondingly low sensitivities in the present study compared to their respective development cohorts. This likely reflects differences in the overall event rate (incidence of a poor outcome was 54 % in the TTM2-trial vs. 79 % in the OHCA-[166] and 74 % in the CAHP development cohorts,[15] respectively) and could probably be improved by simply adjusting the cut-offs. The MIRACLE2-score on the other hand produced risk estimates on par with its development cohort, evident by its specificity levels being similar to those of its development cohort across all defined risk groups.[14] The AUROC estimate was however lower in the present study (0.81 vs 0.90), as were sensitivity levels across the different cut-offs, indicating adequate calibration but decreased discriminatory performance compared to the development cohort, possibly owing to case-mix differences.[14] For the TTM-score, negligible underestimations of risk were seen in the present study compared to its development cohort and a very similar AUROC-estimate.[13]

When shown to provide similarly accurate risk estimates as more complex alternatives, the MIRACLE$_2$-score must be highlighted as an attractive solution for clinical integration. It is not only easier to use a score that is effortlessly summarised from seven items than having to use aids, but also potentially safer. If one factor were to be deviant from several others, this is more easily spotted with fewer variables and simple mathematics.

Like any prediction model, these risk scores would need to be validated in the intended usage population prior to clinical implementation to at the very least accommodate differences in baseline risk.[174] As the TTM-2 trial by its international, multicentre[60] nature represents no single population but rather a mean of multiple, no recalibration attempts were made in paper IV.

8.6 Ethical implications

The results of paper IV show that very high levels of specificity are achievable for especially the MIRACLE2-, TTM- and CAHP-scores in terms of predicting death or a poor functional outcome at 6 months after cardiac arrest, but they do not offer any guidance on which specificity level should be used to predict futility. Papers II and III show that the uTOR offers prognostic information but might be associated with non-negligible inaccuracy when applied on an individual patient level.

One way of dealing with these problems of uncertainty concerning CDRs is to remove them from their scientific context and not considering them from a binary perspective. The outcome of the uTOR might be binary, but the patient is not. What if the uTOR says terminate, but end-tidal CO_2 levels suddenly reaches 4 KPa? Or if the $MIRACLE_2$-score is just 4, but the elderly patient has an early onset status myoclonus while at the same time developing severe cardiogenic chock?

Clinical decision rules should neither be considered rules, nor ready-made decisions. It is the human beings treating their patient who make the decisions they think are best for him or her. But when the best is not obvious, validated and easy-to-grasp risk estimates might provide a good starting point for a holistic patient assessment.

8.7 Limitations

The risk of bias in the assessment of the association between use of automated chest compression devices and survival in paper I has been discussed in a previous section and is acknowledged as one of the main limitations of this paper. It is also acknowledged that without data on how ACC devices were implemented in each EMS (e.g., in all ambulances and used for all cases of cardiac arrest vs. in specialist units reserved for special circumstances), inferences about the implementation of these devices on a system level cannot be made.

Papers II and III share several limitations, of which the most important arguably is that the use of hospital-based registries limits generalisability to the prehospital setting. It is also important to highlight the fact that while the uTOR was not implemented in any of the two studied ambulance services, its components were obvious to everyone involved in resuscitation – thereby fulfilling the prerequisites for self-fulfilling nihilism associated with futility prediction.[183]

For paper III, the lack of recorded timepoints of in-hospital interventions make distinctions between resuscitative measures and routine post-ROSC care impossible, limiting interpretability.

The most important limitation of paper IV is arguably that it is based on a cohort of patients with a suspected cardiac cause of arrest with unwitnessed cases of asystole excluded, thereby limiting the external validity of our results to this population. The time from cardiac arrest until initiation of bystander CPR was not recorded in the TTM-2 trial but no-flow time was part of 3 of the 4 evaluated scoring systems. This was handled by single-imputation of the median value from the first TTM-trial,[59] introducing some uncertainty. While a limitation, it is also a realistic clinical scenario as both timing and quality of bystander CPR are difficult or impossible to estimate. The imputation of a low value for cases with bystander CPR retains the prognostic value of the more precise no-flow interval in cases not receiving bystander CPR while assuming a conservative "best-case"-scenario for patients receiving bystander-CPR. Completely omitting the no-flow interval has also been suggested and both the OHCA- and CAHP-scores have been validated without their no-flow-item.[184]

9 Conclusions

Automated chest compression devices

- The use of automated chest compression devices after OHCA varied substantially between Swedish regions between the years 2011 - 2015.
- Automated chest compression devices, as implemented in Sweden 2011-2015, are on average used in patients with a more severe condition in out-of-hospital cardiac arrest.

Transport with ongoing resuscitation efforts

- Survival is rare among patients transported with ongoing CPR after OHCA.
- The universal termination of resuscitation rule would have prevented futile transports to hospital for about a third of all patients who were transported, but limited specificity in some situations warrants caution.

In-hospital interventions in OHCA

- The additional therapeutic options of the hospital were rarely utilised in patients transported to hospital with ongoing CPR to hospitals without eCPR-protocols, with interventions preceding sustained ROSC in < 1 % of patients.

Early risk prediction after ROSC

- The CAHP-, MIRACLE$_2$- and TTM-scores all showed excellent discriminatory performance after OHCA of suspected cardiac origin.
- Due to its simplicity, the MIRACLE2-score could be a practical solution for clinical application.

10 Future aspects

Implementing termination of resuscitation guidelines in clinical practice

Although criteria for termination of resuscitation are implemented in many EMS systems, multiple studies indicate that compliance is variable.[110,111,160] Although this to some extent is desirable for the reasons outlined in this thesis, non-compliance should ideally be guided only by patient factors. In practice, a multitude of aspects likely influences decisions on whether to transport a patient to hospital or not, and only a few are directly related to patient care.[112,185]

Future research must take these barriers into account and evaluate specific interventions targeting them. With data from regions with well-integrated prehospital physician services showing high levels of TOR without indications of increased overall mortality,[114,186] increased prehospital physician presence could be one such intervention.

Identifying selection criteria for eCPR

The focus of this thesis has been the identification of patients who likely would not benefit from peri-arrest transport to hospital and advanced resuscitation techniques. In a binary world, application of our findings would imply that all patients *not* meeting any set of criteria indicative of a likely poor prognosis *will* benefit from advanced resuscitation techniques. That this is not the case is evident from the results of papers II-IV, where it is obvious that specificity takes priority over sensitivity in futility prediction. For resource-intensive and highly invasive therapies like eCPR, the inverse is needed and has been highlighted as a knowledge gap in the eCPR literature.[138] Ideally, such factors would be derived from a large controlled trial with broad eligibility criteria to minimise bias while at the same time maximising external validity of the results. Given the resource intensity of eCPR and the likely low survival rates associated with a completely unselected patient population, to adequately power such a trial would not be practically feasible – and if it were, its results could pose an ethical challenge. A more realistic approach would be to use a few, unambiguous eligibility criteria such as shockable cardiac arrest with an upper age limit and a protocolised approach for WLST to allow for unbiased investigation of additional selection criteria in the final study population.

11 Svensk sammanfattning

Vi kallar det för hjärtstopp, men det enda vi egentligen vet när en person plötsligt förlorar medvetandet och slutar andas normalt är att blodcirkulationen till hjärnan och dess andningscentrum plötsligt blivit otillräcklig. Den vanligaste orsaken till detta är kranskärlssjukdom, där lokal syrebrist i hjärtmuskeln kan ge upphov till så pass allvarliga rubbningar i hjärtrytmen att hjärtats pumpförmåga helt upphör.

När blodcirkulationen till hjärnan upphävs försvinner också den kontinuerliga syre- och näringstillförsel som krävs för dess och den drabbades överlevnad. Den enda otvetydigt effektiva åtgärden för att återställa viss blodcirkulation är hjärt-lungräddning, som därigenom köper tid tills försök att återstarta hjärtat med en hjärtstartare kan göras. Men även med dessa åtgärder är det tyvärr långt ifrån alla de cirka 6000 svenskar som man årligen försöker återuppliva efter hjärtstopp utanför sjukhus som överlever. Andelen som överlever minst 30 dagar efter utskrivning från sjukhus har fördubblats från ungefär en tjugondel kring millennieskiftet och ligger nu stabilt kring en tiondel.

Det är väl belagt att bröstkompressioner måste ges med tillräcklig kraft och frekvens för att maximalt blodflöde ska uppnås vid hjärt-lungräddning, och man har också visat att livräddare snabbt blir för trötta för att kunna ge bröstkompressioner av god kvalitet under mer än några minuter åt gången. Man har därför utvecklat olika automatiserade medicinsktekniska hjälpmedel som utan uttröttning kan utföra denna livsviktiga behandling, av vilka den svenskutvecklade LUCAS® (Jolife AB / Stryker Medical, USA) är marknadsledande i Sverige. LUCAS® används därför synonymt med automatiserade hjälpmedel för bröstkompressioner i denna text. I stora studier har man trots dessa teoretiska fördelar inte kunnat visa att användning av LUCAS® leder till förbättrad överlevnad efter hjärtstopp utanför sjukhus, men ändå används den av många ambulansorganisationer runtom i Sverige och världen. En anledning till detta kan vara att LUCAS® underlättar transport av patienter med pågående hjärt-lungräddning till sjukhus - något som också görs i stor utsträckning i bland annat Skåne. Det är dock okänt om sådana transporter faktiskt leder till att patienter får tillgång till ytterligare behandling utöver den avancerade hjärt-lungräddning som utförs av ambulanspersonal före och under transport, och om sådan ytterligare behandling i så fall förbättrar överlevnaden.

I en av de studier som ligger till grund för denna avhandling undersökte vi genom ett stort rikstäckande register (Svenska hjärt-lungräddningsregistret) hur LUCAS®

användes i Sverige mellan 2011 och 2015. Våra resultat visade att användningen varierade stort mellan våra 21 regioner och att behandling med LUCAS® främst verkade vara förbehållen patienter med ett svårare sjukdomstillstånd. En anledning till detta skulle kunna vara att man i de fall där man tidigt får igång blodcirkulationen aldrig hinner plocka fram LUCAS®.

I två andra studier undersökte vi patienter som kom in med ambulans till akutmottagningen med pågående hjärt-lungräddning. I den ena studerade vi patienter som transporterades till Skånes universitetssjukhus i Lund under en sexårsperiod 2010 – 2015, och i den andra samarbetade vi med brittiska forskare för att undersöka huruvida ett annat sjukvårdssystem påverkar resultaten genom att studera samma patientpopulation på tre akutsjukhus i och runt Birmingham under en ettårsperiod. Resultaten från båda dessa studier var samstämmiga i att väldigt få (färre än 2 av 100) patienter som transporteras till sjukhus utan att först ha återfått egen cirkulation överlever till utskrivning från sjukhus. Dessutom var det ovanligt att man på sjukhuset utförde någon ytterligare behandling utöver den som redan gavs av ambulanspersonalen. Vi utvärderade också ett beslutsstöd som i tidigare studier visat sig kunna hjälpa ambulanspersonal att förutsäga vilka patienter som inte kommer att överleva, för att stötta dem i det svåra beslut som ett avbrytande av återupplivningsförsök innebär. Våra studier visade att återupplivningsförsök hade kunnat avbrytas före ankomst till sjukhus i ungefär en tredjedel av alla fall, men om man tillämpat beslutsstödet fullt ut skulle man också ha avbrutit återupplivande behandling på två patienter som slutligen överlevde.

Även om varje människas död är en tragedi och vi ständigt gör vårt yttersta för att rädda varje möjligt liv, är det fortfarande väldigt mycket vi inte kan göra och väldigt många tillstånd vi inte kan bota. I dessa fall, när vi ställs inför det faktum att patienten trots den vård vi bedriver inte har en rimlig chans att återhämta sig till värdigt liv, måste vi förr eller senare ge upp försöken till bot för att helt fokusera på lindring. Men att fatta rätt beslut vid rätt tidpunkt kan vara svårt, särskilt om tiden är knapp. Med utgångspunkt i detta studerade vi i vår fjärde studie ett flertal olika *riskprediktionsmodeller* – alltså poängskalor som utvecklats för att väga samman flera olika kliniska parametrar till en sammanvägd uppskattning av en patients risk för ett negativt utfall. I hjärtstoppssammanhang är hjärnan det organ som snabbast tar mest skada, varför det negativa utfallet vi studerade var död eller mycket dålig neurologisk funktionsnivå. Våra resultat visade att alla förutom en av de utvärderade poängskalorna gav bra riskuppskattningar, med mycket små skillnader sinsemellan. En av dem är till sin uppbyggnad betydligt lättare att använda och överskåda än de andra, varför den sannolikt vore det bästa valet om man skulle introducera någon av dem i klinisk praxis.

Sammantaget tyder våra resultat på att många patienter utsätts för utsiktslös behandling och att de olika utvärderade beslutsstöden skulle kunna bidra till mer välinformerade beslut i framtiden, men då endast som en del i en fullständig bedömning av patientens tillstånd.

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