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CARDIAC ARREST – RISKS AND OUTCOMES

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Cardiac arrest – risks and outcomes

Abstract

About 10000 individuals suffer a cardiac arrest (CA) in Sweden every year. Approximately 1/10 survives if the CA occurs outside of the hospital while 3/10 survives if the arrest occurs within the hospital. Little is known about which comorbidities and acute conditions that affect survival the most and currently there are no effective scoring systems to help physicians to assess the chances of survival. There is also scarce evidence about which risk factors, including genetics, that predict the risk of future CA in a healthy population.

In paper I, all in-hospital CA occuring between 2007-2010 at Malmö University Hospital (n=287) were analysed with regard to survival, taking comorbidities and acute conditions into consideration. Pre-Arrest Morbidity score (PAM) and Prognosis After Resuscitation score (PAR) were calculated for each patient. We found that age, malignancy, poor functional status, hyponatremia and elevated heart rate were associated with poor survival. The PAM- and PAR-score had an overall low accuracy to predict survival.

In paper II, the "Good Outcome Following Attempted Resuscitation" score (GO-FAR) was evaluated on the same cohort. The GO-FAR score was designed to assess the chance or survival with Cerebral Performance Category (CPC) = 1. Our results showed that the score had a high accuracy of estimating chance of survival, even when applied on a population with different demographics than originally investigated.

In paper III we investigated midlife risk factors for future CA in a healthy population by means of combining the Malmö Diet and Cancer-study (MDC) (n=30447) with the local cardiac arrest registry (n=2758). The study had a follow-up time of 17.6 years (SD 4.6) and during this period 378 cases of CA occurred. Smoking, dyslipidemia, diabetes and previuos heart failure, cardiovascular- or cerebrovascular disease increased the risk of future CA of cardiac aetiology, while smoking, hypertension and obesity were the most important risk factors for future CA of non-cardiac aetiology.

In paper IV, we investigated the risk of future CA in relation to a genetic risk score (GRS) for cornary artery disease. The same cohort was used as in paper III but with those patients with prevalent heart failure, cardiovascular- or cerebrovascular disease excluded. A total number of 23300 subjects remained out of which 252 CAs occurred during a 18.9 year (SD 4.4) follow-up. Multivariate analysis showed a clear association between the GRS and CA of cardiac aetiology but no such association between the GRS and CA of non-cardiac aetiology. Further analyses were therefore directed towards CA of cardiac aetiology (n=181). A composite score consisting of low-, medium- and high genetic risk together with traditional cardiovascular risk factors was created. The composite score was divided into deciles and further into groups of low- (D1-3), medium- (D4-9) and high risk (D10). Comparison of the groups of high- versus low risk, yielded a hazard ratio (HR) of 82.19 {(95% CI 20.07-336.69) (P<0.001)} for future CA.

Key words Cardiac arrest, risk, cardiopulmonary resuscitation (CPR), score, obesity, genetic risk score (GRS)		
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CARDIAC ARREST – RISKS AND OUTCOMES

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To my father Kjell. I miss you and I miss your laughter

Contents

List of publications

Paper I: Ohlsson MA, Kennedy LM, Juhlin T, Melander Olle. Evaluation of pre-arrest morbidity score and prognosis after resuscitation score and other clinical variables associated with in-hospital cardiac arrest in southern Sweden. Resuscitation. 2014 Oct;85(10):1370-4

Paper II: Ohlsson MA, Kennedy LM, Ebell MH, Juhlin T, Melander Olle. Validation of the "Good Outcome Following Attempted Resuscitation" score on in-hospital cardiac arrest in southern Sweden. *Int J Cardiol.* 2016 Oct 15;221:294-7

Paper III: Ohlsson MA, Kennedy LM, Juhlin T, Melander Olle. Midlife risk factor exposure and incidence of cardiac arrest depending on cardiac or non-cardiac origin. *Int J Cardiol.* 2017 Aug 1;240:398-402

Paper IV: Ohlsson MA, Kennedy LM, Juhlin T, Melander Olle. Risk prediction of future cardiac arrest by evaluation of genetic risk score alone and in combination with traditional risk factors. Manuscript

Abbreviations

ACLS	Advanced Cardiac Life Support
ADL	Activities of daily life
AED	Automated External Defibrillator
AMI	Acute myocardial infarction
APACHE	Acute Physiology and Chronic Health Evaluation
ApoA1	Apolipoprotein A1
ApoB	Apolipoprotein B
AS	Asystole
AU-ROC	Area under the receiver operating characteristic
BMI	Body mass index
CA	Cardiac arrest
CAD	Coronary artery disease
CABG	Coronary artery by-pass grafting
CCU	Coronary care unit
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CPC	Cerebral performance category
CPR	Cardiopulmonary resuscitation
DNR	Do-not-resuscitate
DNAR	Do-not-attempt resuscitation
ECG	Electrocardiogram
EMS	Emergency Medical Services

ER	Emergency room
ERC	European Resuscitation Council
GO-FAR	Good Outcome Following Attempted Resuscitation
GRS	Genetic Risk Score
GWAS	Genome-wide Association Study
HRT	Heart rate
HR	Hazard ratio
ICU	Intensive care unit
IHCA	In-hospital cardiac arrest
IKVM	Institutionen för kliniska vetenskaper i Malmö
IQR	Interquartile range
LU	Lund university
LUCAS	Lund University Cardiac Arrest System
MI	Myocardial infarction
MDCS	Malmö diet and cancer study
NSTEMI	Non-ST elevation myocardial infarction
OHCA	Out-of-hospital cardiac arrest
OR	Odds ratio
PAM	Pre-arrest morbidity
PAR	Prognosis after resuscitation
PCI	Percutaneous coronary intervention
PCR	Polymerase Chain Reaction
PEA	Pulseless electrical activity
RCT	Randomized Controlled Trial
ROC	Receiver operating characteristics
ROSC	Return of spontaneous circulation
SCAR	Swedish cardiac arrest registry

SCD	Sudden cardiac death
SD	Sudden death
SD	Standard deviation
SNP	Single Nucleotide Polymorphism
STEMI	ST-elevation myocardial infarction
SUS	Skåne university hospital
USA	United States of America
VF	Ventricular fibrillation
VT	Ventricular tachycardia

Introduction

Historical background

The idea of potentially reversing sudden death has a long history and is believed to be as old as human history [1]. One of the first descriptions is found in Egyptian mythology where Isis is depicted blowing air into Osiris mouth, thus resurrecting him [2]. In Egypt the "inversion method" for resuscitation was developed about 1500 B.C [1]. According to this method, the patient was hung upside down while the chest was compressed and then released [3]. Other sources, such as the Book of Exodus, includes a description of a Hebrew midwife that resuscitates a new-born by blowing air into the child's mouth [4].

During the middle ages the development of resuscitation was stalled [3] and did not evolve further until Andreas Vesalius described his artificial ventilation in the 16th century [5]. In 1744, the Scottish surgeon William Tossach described a successful resuscitation of a coal miner by means of mouth-to-mouth ventilation [6]. After this description, the Paris Academy of Sciences soon recommended the mouth-to-mouth resuscitation technique for victims of drowning [7]. In the following years the mouth-to-mouth technique became challenged, partly due to hygienic reasons, and because of this manual methods of ventilation developed such as bellow ventilation and mouth-to-mask ventilation [8].

During the late 19th century different methods of cardiac massage started appearing [8]. The German surgeon Friedrich Maass is believed to be the first who successfully resuscitated a patient with closed chest cardiac massage in 1892 [3] and in 1901 the first open chest cardiac massage was described by the Norwegian physician Kristian Igelsrud [9].

Since 1791 it had been known that electricity could elicit muscle contractions as shown by Galvani [9]. Almost a decade later, in 1889, Professor John McWilliam hypothesized that ventricular fibrillation preceded death in humans [10]. This was followed by the experiments by Williem Einthoven who in 1901 invented the string galvanometer, which became the first electrocardiogram [11]. These discoveries laid the foundation for the breakthrough in 1947, when cardiac surgeon Claude Beck during surgery successfully applied defibrillation on ventricular fibrillation diagnosed by ECG and successfully resuscitated the patient

[12]. Eight years later, in 1955, Paul Zoll performed the first closed-chest defibrillation in humans [13, 14].

The development of modern cardiopulmonary resuscitation

In 1958, Safar and McMahon published a paper that for the first time introduced the modern mouth-to-mouth artificial ventilation still used today [15] (figure 1).
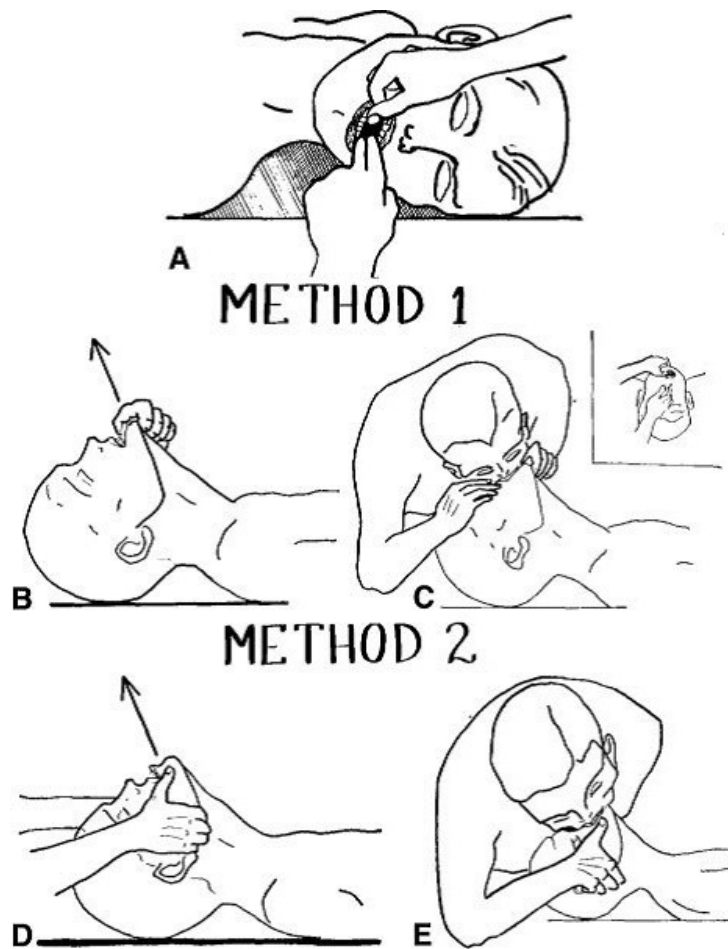
Figure 1. Figure from publication by Cooper et al illustrating the need for neck extension and jaw thrust to maintain the airway during mouth-to-mouth artificial ventilation (14). © Wolters Kluwer Health, Inc. Reprinted with permission.

In 1960, the next big step occurred when Kouwenhaven et al, unaware of the research by Dr Maas [3], reintroduced the concept of external cardiac massage in cardiac arrest [16]. This enabled the therapy to be applied outside of the operating room where it until this point had been limited [16].

In 1966, the first cardiopulmonary resuscitation (CPR) guidelines were published in USA but it would not be until 1970, education of the general public occurred. Cobb, Kopass and Eisenberg implemented a project in Seattle, USA, in which 100 000 citizens were instructed to perform CPR [14]. Training of laypersons was formally initiated in 1974 [17] and in 1976 the first training courses in Advanced Cardiac Life Support (ACLS) were held[9].

In 1991 the "chain of survival" (figure 2) was introduced. It consisted of four links; early access (alerting emergency medical service), early CPR, early defibrillation and early ACLS [14]. This concept is still used today.

Figure 2. The chain of survival. From European Resuscitation Council guidelines for Resuscitation 2010 Section 1 by Monseiurs et al (23). © Elsevier Ireland Ltd. Reprinted with permission.

Cardiac arrest

Definition and pathophysiology

Cardiac arrest is defined as "the cessation of cardiac mechanical activity as confirmed by the absence of signs of circulation" [18]. If not treated with CPR, the condition will progress to death [19]. Death, according to Swedish law, is in turn defined as "when all functions totally and irreversibly have been lost from all the parts of the brain, i.e total brain infarction" [20].

Weisfeldt and Becker have described three different phases of cardiac arrest in 2002. The first is the "electrical phase" which lasts for approximately 4 minutes. It is followed by the "circulatory phase" which lasts from 4 to 10 minutes. Finally the "metabolic phase" occurs in which global ischemia causes tissue injury and circulating metabolic factors cause additional injury[21].

Four types of different arrhythmias can be encountered in cardiac arrest, out of which ventricular fibrillation (VF) is the most common. Other manifestations include ventricular tachycardia (VT), pulseless electrical activity (PEA) and asystole (AS) [22]. The latter two cannot be treated with defibrillation while both VF and VT are considered to be "shockable rhythms" [23].

Classification according to aetiology

The main cause of cardiac arrest is cardiac disease, which accounts for 67-82% of the cases depending on source [24, 25]. This group is dominated by coronary artery disease (CAD) followed by heart failure and arrhythmia [26].

The non-cardiac aetiologies includes trauma, non-traumatic bleeding, intoxication, near drowning and pulmonary embolism [27].

Classification according to location

Cardiac arrest is commonly subdivided into in-hospital cardiac arrest (IHCA) and out-of-hospital cardiac arrest (OHCA) [23].

Epidemiology

Sudden cardiac arrest is reported to affect between 350 000 to 700 000 individuals in Europe per year with an incidence of 0.4-1/1000 inhabitants and year [28]. In a study by Berdowski et al, the incidence of emergency medical services (EMS)-attended OHCA (per 100,000 person-years) was reported to differ globally with 52.5 for Asia, 86.4 for Europe, 98.1 for USA and 112.9 for Australia [29]. The incidence of IHCA is reported to be 1-5/1000 admissions [25].

Risk factors

Little is known about risk factors of future cardiac arrest. Previous studies have investigated the concept of "sudden (cardiac) death" (SD, SCD) and found that classical cardiovascular risk factors such as diabetes, hypertension, smoking, dyslipidemia, heredity and obesity increased the risk [30-32].

Few studies have investigated the differences between cardiac arrest of cardiac aetiology and those of non-cardiac aetiology. In one study from 2003 by Engdahl et al, it was noted that those suffering from a cardiac arrest of non-cardiac aetiology had lower survival rates, lower occurrence of VF and witnessed cardiac arrest compared to those of cardiac aetiology. Further it was observed that the patients with non-cardiac aetiology had a higher occurrence of chronic alcohol abuse and chronic obstructive pulmonary disease (COPD), but lower occurrence of cardiovascular disease such as hypertension, diabetes, previous myocardial infarction (AMI), stroke and congestive heart failure [33]. Independent risk factor models for cardiac arrest depending on aetiology have not previously been described.

Treatment

Cardiac arrest is treated by the means of CPR. The algorithm has developed through the years and the latest version of it from the 2015 guidelines by the European Resuscitation Council (ERC) [23] is presented in figure 3.

EUROPEAN RESUSCITATION COUNCIL

Advanced Life Support

Unresponsive and not breathing normally?

Call Resuscitation Team

CPR 30:2
Attach defibrillator/monitor
Minimise interruptions

Assess rhythm

**Shockable
(VF/Pulseless VT)**

**Non-shockable
(PEA/Asystole)**

1 Shock
Minimise interruptions

Return of spontaneous circulation

Immediately resume CPR for 2 min
Minimise interruptions

IMMEDIATE POST CARDIAC ARREST TREATMENT
- Use ABCDE approach
- Aim for SaO_2 of 94-98 %
- Aim for normal $PaCO_2$
- 12 Lead ECG
- Treat precipitating cause
- Targeted temperature management

Immediately resume CPR for 2 min
Minimise interruptions

DURING CPR
- Ensure high quality chest compressions
- Minimise interruptions to compressions
- Give oxygen
- Use waveform capnography
- Continuous compressions when advanced airway in place
- Vascular access (intravenous or intraosseous)
- Give adrenaline every 3-5 min
- Give amiodarone after 3 shocks

TREAT REVERSIBLE CAUSES
Hypoxia
Hypovolaemia
Hypo-/hyperkalaemia/metabolic
Hypothermia/hyperthermia

Thrombosis – coronary or pulmonary
Tension pneumothorax
Tamponade – cardiac
Toxins

CONSIDER
- Ultrasound imaging
- Mechanical chest compressions to facilitate transfer/treatment
- Coronary angiography and percutaneous coronary intervention
- Extracorporeal CPR

Figure 3. Algorithm for Advanced Life Support from European Resuscitation Council guidelines for Resuscitation 2010 Section 1 by Monseiurs et al (23). © Elsevier Ireland Ltd. Reprinted with permission.

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The chest compression depth is recommended to be approximately 5 cm and not deeper than 6 cm. A compression depth of 4.5-5.5 cm has shown to be associated with better outcomes [34-36]. The rate of chest compressions has also been studied and according to the current guidelines a compression rate of 100-120 per min has shown to improve survival rates [37, 38] and is now recommended.

Depending on which rhythm is present, shockable- (VF or VT) or non-shockable (PEA/AS) rhythm, one of the two arms shown in figure 3 is followed accordingly. Administration of Adrenaline every 3-5 minutes and Amiodarone after three shocks are the only drugs that currently are recommended during CPR [23]. This recommendation remains despite the fact that several studies have shown increased rates of return of spontaneous circulation (ROSC) but no significant difference in survival in those receiving adrenaline [39-43] compared to those who did not receive adrenaline.

If ROSC can be established, the medical care continues into the post-resuscitation care constituting the fourth link in the chain of survival. This area has evolved greatly during the last years and appeared in the ERC guidelines for the first time in 2005 [44]. The term "post-cardiac arrest syndrome" is being used to describe the combination of brain injury, myocardial dysfunction, systemic ischemia/reperfusion response and persistent precipitating pathology [45]. The treatment taking place at the intensive care unit (ICU) focuses on optimizing airway, breathing and circulation as well as neuroprotective measures such as glucose control and temperature control [23]. Maintaining blood glucose at ≤ 10 mmol/L and avoidance of hypoglycaemia has been shown to improve neurological outcome [46, 47]. Concerning temperature control, a period of hyperpyrexia commonly occurs in the first 48 hours after cardiac arrest [48, 49]. This has been shown to be associated with poor outcomes [50, 51]. The current recommendation is therefore to maintain temperature between 32° C and 36° C [23]. Studies from 2002 have shown a benefit in both survival and neurological outcome when keeping temperature as low as 32° C to 34° C [52, 53], while more recent studies such as the TTM trial [54-56] did not show any benefits regarding survival, cognitive and neurological status when comparing 33° C to 36°C.

Survival

The initial study by Kouwenhoven et al [16] was followed by another study in which survival rates of cardiac arrest were as high as 77% [57]. A subsequent study of a larger size including 118 patients showed a marked reduced survival of 24% [58].

Other sources claim survival rates between 2% to 25% for OHCA [59-61] and 0% to 29% for IHCA [62, 63]. In recent years the survival of OHCA has increased

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from 5.7% in 2005-2006 to 9.8% in 2012 [64]. The survival of IHCA has also increased from 18.1% in 2000-2003 to 21.4% 2007-2010 [65]. Recent Swedish data from 2015 show somewhat higher survival rates with 31% for IHCA and 11% 30-day survival for OHCA [66].

Survival also greatly depends on the type of arrhythmia present [29, 66, 67], the greatest difference being between shockable (VF/VT) and non-shockable rhythm (PEA/AS) where shockable rhythm is associated with higher survival rates [68, 69].

Differences in survival have also been observed depending on cardiac or non-cardiac aetiology in a study by Snipelisky et al, in which the group of cardiac aetiology had a survival to discharge of 34.4% vs 13.8% (p=0.0018) in the group of non-cardiac aetiology [70]. This finding has been reproduced in other studies [33, 71].

Long-term survival for IHCA has only been investigated in a few studies and ranges from 58.5-86% at 1-year and 41-71% at 3-years [72-76]. For OHCA, long-term survival ranges from 68.2-88% at 1-year, 52.8-81% at 3-years and 65-79% at 5-years [77-80].

Neurological and cognitive outcome

About 2/3 of the patients suffering OHCA and 22.9% of patients suffering IHCA die from neurological damage [81]. The cerebral performance category (CPC) scale is the gold standard [82] for estimation of neurological status after survival of cardiac arrest [83]. In table 1 the scale is described.

Table 1
Cerebral performance category scale

CPC 1	Good cerebral performace: conscious, alert, able to work, might have mild neurological or psychological deficit
CPC 2	Moderate cerebral disability: conscoius, sufficient cerebral function for independent activities of daily life. Able to work in a sheltered environment
CPC 3	Severe cerebral disability: conscious, dependent on others for daily support because of impaired brain function. Ranges from ambulatory state to severe dementia or paralysis
CPC 4	Coma or vegetative state
CPC 5	Brain death

CPC 1-2 has traditionally been regarded as a "good neurological outcome" and CPC 3-4 as "poor outcome" [84].

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More than 90% of the survivors of cardiac arrest have CPC 1-2 at discharge from hospital [66], while other claim significant neurological [85] and cognitive impairments [86, 87] as well as impairments of level of functioning and quality of life after survival of cardiac arrest [88]. Increasing age seems to be associated with worse neurological outcome [89, 90].

Complications to CPR

CPR is a physically strenuous treatment. Several studies show how it is complicated by painful fractures of ribs and sternum, pneumonia and periods of prolonged mechanical ventilation [91-93]. By reviewing forensic records, rib fractures were found in 29% and sternal fractures in 14% of patients in a study by Black et al [94]. In another study the prevalence of sternal fractures was lower (8.1%) but the prevalence of rib fractures much higher at 70% [95]. In both studies an increased prevalence of rib fractures was associated with older age [94, 95].

Pre-arrest assessment

Development of scoring systems

Few studies have investigated pre-arrest risk factors associated with survival, both concerning OHCA and IHCA. In 1981 the Acute Physiology and Chronic Health Evaluation (APACHE) system was proposed in an article by Knaus et al [96]. This score aimed to evaluate severity of illness and to prognose all-cause mortality in patients in an ICU. In 1985 the score was further developed and APACHE II was proposed [97], followed by APACHE III in 1989 [98] and APACHE IV in 2006 [99].

These scores were not specifically designed for estimation of prognosis in the setting of cardiac arrest but in 1989 the "pre-arrest morbidity" (PAM) score (table 2) was devised by George et al [100] and its purpose was to assist doctors and patients to make an informed decision about prognosis after CPR. The score was further developed in 1992 when Ebell et al [101] proposed the "prognosis after resuscitation" (PAR) score (table 2).

Table 2
PAM- and PAR-score

Variable		PAM	PAR
Malignancy		3	
	Metastatic		10
	Non-metastatic		3
Sepsis (on admission)		1	5
Homebound		3	5
Pneumonia (on admission)		3	3
Creatinine			
> 220 mmol/l		3	
>130 mmol/l			3
Age > 70 years			2
Acute MI		1	-2
Hypotension		3	
Heart failure		1	
Angina pectoris		1	
Gallop rhythm		1	
Oliguria		1	
Assisted ventilation		1	
Coma		1	
Acute stroke		1	
Cirrhosis		1	

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The PAM-, PAR- and APACHE III-scores were evaluated and compared as to accuracy in predicting outcomes of CPR in IHCA in a study by Ebell et al in 1997 [102]. In this study, the PAR- and APACHE III-score performed the best, although AU-ROC values greater than 0.60 were not achieved, consistent with relatively poor discrimination.

Despite the failure of composite scoring systems at this point, a meta-analysis from 2011 [103] including a total of 96 499 patients managed to identify important clinical variables associated with poor outcome in the instance of IHCA such as metastatic or haematological malignancy {Odds Ratio (OR) 3.9}, age over 70, 75 or 80 years (OR 1.5, 2.8 and 2.7 respectively), altered mental status (OR 2.2), dependent Activities of Daily Life (ADL) (range 3.2-7.0, depending on activity), renal insufficiency (OR 1.9), hypotension on admission (OR 1.8), admission for pneumonia (OR 1.7) or medical non-cardiac diagnosis (OR 2.2). Other studies have confirmed these results by showing an independent association between in-hospital mortality and advanced age, Afro-American ethnicity, non-cardiac illness, non-surgical illness, malignancy, acute stroke, trauma, septicaemia and hepatic insufficiency [104-106]. Also diabetes mellitus and heart failure have been shown to be associated with poor outcome [107, 108]. Factors that have been shown to improve survival are cardiac diagnosis, presence of ST-elevation myocardial infarction (STEMI) and cardiac monitoring [103, 109-111].

In 2013, a new scoring system named Good Outcome Following Attempted Resuscitation (GO-FAR) (table 3) was proposed in a study by Ebell et al [112]. It was based on 51 240 cases of IHCA and its purpose was to assess probability of survival with intact neurological function defined as CPC=1. In this study accuracy was improved as compared to other scoring systems with an AU-ROC of 0.78.

Table 3
GO-FAR score

Variable	Score
Neurologically intact at admission (CPC=1)	-15
Major trauma	10
Acute stroke	8
Metastatic or hematologic cancer	7
Septicemia	7
Medical non-cardiac diagnosis	7
Hepatic insufficiency	6

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Admitted from skilled nursing facility	6
Hypotension or hypoperfusion	5
Renal insufficiency or dialysis	4
Respiratory insufficiency	4
Pneumonia	1
Age (years)	
70-74	2
75-79	5
80-84	6
≥ 85	11

Pre-arrest assessment of the elderly undergoing CPR following OHCA was performed in a study by van de Glind in 2013 [113]. The study aimed to assess pre-arrest factors for survival, quality of life and functional outcome to enable the patients to more accurately make decisions about the appropriateness of CPR. The initial attempt of a meta-analysis was not successful due to high heterogeneity in reporting and statistics. Increased age was overall negatively associated with survival and only two studies included a pre-arrest assessment of comorbidity. Furthermore, the results concerning quality of life were contradictory as well as scarse. Three studies reported the quality of life after successful resuscitation as lower when compared to a control [114-116], while others reported it unchanged [117, 118].

The role of genetics in risk prediction of cardiac arrest – part of the future?

Many studies have investigated genetic abnormalities associated with sudden cardiac death. These mainly include arrhythmogenic abnormalities such as long-QT-syndrome, Brugada syndrome and ion channelopathies [119-124].

The relationship between genetics and coronary heart disease (CHD) is well known [125-127] but few studies have investigated a link between genetic risk of CHD and SCD [128, 129]. In 2015 a genetic risk score (GRS) for CHD was tested against SCD in a study by Hernesniemi et al [130], showing a significant association between the two.

CPR and cardiac arrest in Sweden

In 1983 a working group dedicated to CPR within the Swedish Association of Cardiology was created and standardized courses in CPR were initiated in Sweden [131, 132]. Five years later, in 1988, courses in ACLS were started but were at that time only directed towards personal at ICUs, coronary care units (CCU), emergency rooms (ER) and operating wards [133]. In 2006 focus was shifted to include all physicians and other health care personnel [134].

Since 1990, OHCAs has been registered nationally in the Swedish Cardiac Arrest Registry (SCAR) and since 2005 also IHCAs have been included. To date, the registry comprises 82 697 cases of OHCA and 20 136 cases of IHCA [135].

Since 2009, there has also existed a national registry of Automated External Defibrillators (AED). The number of registered AEDs sold outside of hospital was 43 251 by which 9 923 were registered at the end of 2015 [135].

Survival at 30 days in OHCA has increased from 4.2% in 2000 to 11% in 2015. This is thought to be an effect of improvement in all four links in the chain of survival such as earlier alert to emergency medical services (EMS), greater proportion of bystander CPR, increase in public access AEDs and finally improvements in the post-resuscitation care [136].

Concerning IHCA the rates of survival at 30 days have been approximately 15% for several decades but since 2009 it has increased to about 29-30% [135]. The reason for this increase is primarily thought to be a better selection of patients among whom CPR is initiated [137].

Lund University Cardiac Arrest System (LUCAS) is a gas-driven mechanical compression device [138]. It is in use today in several Swedish cities and has previously shown benefit primarily during ambulance transports [139, 140]. LUCAS was mentioned for the first time in the 2010 guidelines from ERC [138]. Since then randomized controlled trials (RCTs), among them the LINC trial [141], the PARAMEDIC trial [142] and the CIRC trial [143], have not shown any benefits in survival compared to manual compressions. Mechanical compressions are therefore, according to the 2015 ERC guidelines, only recommended in certain situations such as CPR in a moving ambulance, prolonged CPR and CPR in certain procedures (coronary angiography or preparation for extracorporeal CPR) [23].

The clinical problem – Ethics and do-not-resuscitate orders

CPR is a potentially life-saving therapy in the event of cardiac arrest. In 1968 an article was published in which the agony of repeated resuscitations and prolonged death was described [144]. In a study by Dans et al [145] survival to discharge after IHCA was studied from 1965-1985 and during this period survival decreased from 24% to 14%. The authors discuss that survival rates decreased due to the fact that CPR had become more a more widespread treatment and applied in more patients regardless of their underlying condition and prognosis. Thus, the discussion of who benefits and who does not benefit from CPR began. In 1976 the first articles were published in which do-not-resuscitate (DNR) orders were openly discussed [146, 147] and have since then caused much controversy [148].

About 18-82% of hospitalized patients have DNR orders [149-152]. There are important differences between hospitals; in several studies greater than ten-fold variations in DNR orders have been observed [153-155]. Differences in DNR orders have also been described in patients with different diseases but similar prognosis [156]. Increasing age is consistently associated with higher DNR order rates [157] as well as Caucasian race versus Afro-American [158].

Physicians rarely inform the patients about DNR-orders and also do not acquire the opinion of the patients [159, 160]. Several studies show that most patients actually welcome a discussion with their physician about DNR-orders [161-163]. Studies also show that patients often want a large amount of information about their condition but to a much smaller degree want to make medical decisions for themselves [164-167].

A bioethical consensus started to emerge in the early 80's, in which patient's autonomy was emphasized [168]. In the Swedish Law of Health and Medical Care from 1982, it is stated that that "the medical care, as much as possible, should be planned and executed by consulting the patient" [169]. In the report called Ethical guidelines for CPR [170] from the Swedish council of CPR and the Swedish Medical Association, it is stated that DNR-orders can be considered in three different scenarios:

1. It is the wish of the patient

2. The responsible doctors considers CPR to be futile

3. The responsible doctor considers that CPR would not benefit the patient, even if there is a possibility of restoring spontaneous breathing and circulation

The opinion of the patients is imperative when discussing strategies of CPR, regardless if it concerns DNR-orders or not. In Sweden, the strategy of the individual patient is, at the end, a medical decision, although patients and relatives should be informed [170]. Several studies [171-173] have shown that patients overestimate their chances of survival in case of cardiac arrest. In these studies the chances of survival are estimated to be 50% or more. This misconception is speculated to originate from the portrayal of CPR on television according to a study by Diem et al [174]. Also physicians' estimations have shown to be inaccurate, in one study rendering an AU-ROC=0.48, thus equal to random chance [175]. This illuminates the need for patient's education in the matter, which in turn requires more accurate prediction models available to the physicians to adequately guide the patients to make informed decisions.

Aims of the thesis

The aims of the individual studies presented in this thesis were as follows:

Paper I

To evaluate the PAM- and PAR score on all cases of IHCA occurring in Malmö 2007-2010 as well as to investigate new clinical variables of potential use in the risk assessment of in-hospital mortality after IHCA.

Paper II

To validate the GO-FAR score on a Swedish cohort suffering IHCA with different demographics than originally investigated

Paper III

To investigate midlife risk factors for incident cardiac arrest depending on cardiac or non-cardiac aetiology.

Paper IV

To investigate the potential relationship between a genetic risk score for coronary heart disease and incident cardiac arrest adjusted for classical cardiovascular risk factors.

Materials and methods

Paper I

All patients suffering a cardiac arrest at Malmö University Hospital between 2007 and 2010 were registered. Data was obtained from the local cardiac arrest registry and a total of 825 cases were registered. Each case was then reviewed by a medical doctor by access to the medical records software Melior and 538 cases were excluded due to the following reasons: 477 were OHCA, 8 were duplicates, 9 were patients < 18 years of age, 30 were not real cardiac arrests, 6 were cancelled prematurely, 6 were suicides and 2 cases were excluded due to missing data. A total number of 287 cases remained for further analysis.

The local cardiac arrest registry at Skåne University Hospital, Malmö, was created in 1999. All suspected cases of cardiac arrest result in initiation of an automatic alarm, which reaches an emergency team. After completing the resuscitation, data from each case is registered and sent to the local cardiac arrest registry. A specialized nurse reviews the data, additional data required is then collected from the medical records and a report is sent to the national cardiac arrest registry including information about outcome, initial cardiac rhythm, time to defibrillation and place of the arrest noted.

This study was designed as a retrospective observational study. PAM- and PAR-scores along with other clinical variables were calculated and registered for each patient upon admission to the hospital. The variable "Sepsis" was subdivided according to international guidelines [176], "Acute myocardial infarction" was subdivided according to presence or absence of ST-segment elevation on a diagnostic electrocardiogram. The variable "Homebound" was subdivided into "Living at nursing home", "Daily assistance" and "Independent ADL". Sex, age and peri-arrest factors such as initial rhythm and cardiac monitoring was recorded. The pre-arrest variables investigated are presented in table 4.

Table 4.

Variables investigated (% missing values)

Variable	Variable continued
Cardiac rhythm* (0)	Exacerbation of COPD* (0)
Heart rate* (bpm) (0)	Sepsis according to SIRS* (0)
Blood pressure* (mm/Hg) (10.8)	Severe Sepsis* (0)
Pulse oxymetry* (%) (17.8)	Septic shock* (0)
Plasma creatinine* (mmol/L) (19.2)	Pulmonary embolism* (0)
Plasma C-reactive protein* (mg/L) (24.4)	Diabetes Mellitus (0)
Plasma Hemoglobin* (g/L) (16.4)	Independent ADL (0)
Plasma Sodium* (mmol/L) (15.3)	Daily assistance (0)
Plasma Potassium* (mmol/L) (16.7)	Living at nursing home (0)
Respiratory acidosis* (54)	Chronic ischemic heart disease (0)
Metabolic acidosis* (46.3)	Hypertension (0)
pH in ABG* (56.4)	Chronic heart failure (0)
BE in ABG* (57.5)	Peripheral artery disease (0)
Plasma Lactate* (mmol/L) (71.4)	Chronic kidney disease (0)
Acute renal failure* (8)	Chronic cerebrovascular disease (0)
STEMI* (0)	COPD (0)
NSTEMI* (0)	Dementia (0)
Unstable angina* (0)	Surgical procedure within the last 4 weeks (0)
Non-invasive ventilation* (0)	Malignancy (0)
Mechanical ventilation* (0)	Metastatic malignancy (84.7)

*=measured upon admission

ABG=Arterial blood gas, BE=Base excess, STEMI=ST-elevation myocardical infarction

NSTEMI=non ST-elevation myocardial infarction, COPD=Chronic obstructive pulmonary disease

SIRS=Systemic inflammatory response syndrome, ADL=Activities of daily life

Variables with missing values exceeding 20% were excluded from further analysis. Survival to discharge was then compared to the remaining clinical variables and the PAM- and PAR-scores respectively.
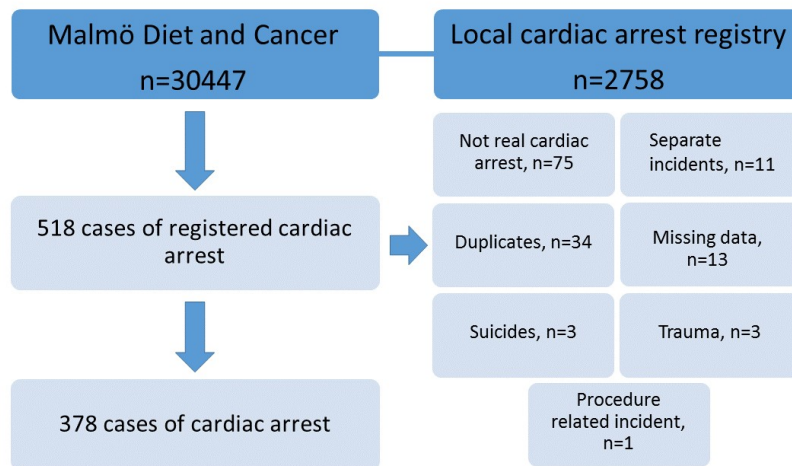
Paper II

All cases of IHCA at Malmö University Hospital 2007-2010 from Paper I were reanalysed with respect to CPC-scores and GO-FAR-score. A total number of 287 cases were included.

This study was designed as a retrospective observational study containing those 287 cases of IHCA initially investigated in Paper I. Through access to medical records software Melior, GO-FAR-score upon admission and CPC-score upon admission and upon discharge for survivors was calculated. Survival to discharge with CPC=1 was then compared to the initial GO-FAR-score.

Paper III

The local cardiac arrest registry from Skåne University Hospital, Malmö (n=2758), was crossed-matched with the Malmö Diet and Cancer (MDC)-cohort (n=30447) using the Swedish personal identification number. The Malmö Diet and Cancer study (MDCS) is a community-based, prospective observational study of 30,447 participants drawn from ~230,000 residents of Malmö, Sweden. Between 1991 and 1996, women aged 45 to 73 years and men aged 46 to 73 years were invited to participate. At that time there were 74138 individuals within the specified age interval available in the Malmö area [177]. Individuals were recruited by means of advertising in papers and at health care centres as well as by personal invitations. The baseline investigation included anthropometry, blood pressure measurement, a physical exam and blood sampling including measurement of apolipoproteins. Participants also completed a questionnaire in which they answered questions about their diet, socioeconomic factors, lifestyle, current medication, current health and previous diseases. More details of the MDC design have been previously reported [177, 178].

We found 518 cases of incident cardiac arrest in the MDC-cohort and each case was reviewed by a medical doctor by access to the medical records software Melior. Seventy-five cases were not real cardiac arrests but rather syncopes, seizures, non-pulseless VTs or bradycardias and therefore excluded from the study. In 11 cases the patient had 2 or more separate cardiac arrest out of which only the first was included. After exclusions a total number of 378 cases of incident cardiac arrest remained. The study design and exclusions are represented in figure 4.

Figure 4. The study design of paper III

By reviewing the autopsy reports of each individual case, the cause of death was established. In those cases where no autopsy had been performed, the cause of death was only recorded if clinically determined as SCD according to the definition described in a study by Muller et al: "the arrest should have occurred within 24 hours after onset of any symptoms that could retrospectively be interpreted as being of cardiac origin" [179]. In cases where the cause of death was not clinically determined nor autopsy was performed, we used the Utstein definition of cardiac arrest of cardiac origin: "an arrest is presumed to be of cardiac aetiology unless it is known or likely to have been caused by trauma, submersion, drug overdose, asphyxia, exsanguination or any other non-cardiac cause as best determined by rescuers" [18]. According to these definitions, all the cases of cardiac arrest were then divided into arrest of cardiac or non-cardiac aetiology.

Relevant baseline exposure data were obtained from the MDCS baseline exam whereas factors with close temporal relationship to the cardiac arrest were collected from the local cardiac arrest registry and additional data related to the cardiac arrest were collected from the medical records. Variables with missing values exceeding 20% were excluded from analysis.

This study was designed to retrospectively investigate cardiac arrest in a prospective study that is MDCS. The baseline data were related to incident cardiac arrests depending on aetiology.

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Paper IV

A genetic risk score (GRS) consisting of 50 single nucleotide polymorphisms (SNPs) was elaborated in a study by Tada et al in 2016 [180]. Twenty-seven of these SNPs were previously included in a GRS by Mega et al [181]. All of the SNPs included had been shown to be associated with coronary heart disease (CHD) in genome-wide association studies (GWAS) [180, 182]. The previously reported risk estimates for the allele of each SNP was natural log transformed and multiplied by one for heterozygotes and two for homozygotes, the products were then summed into a total GRS score [180].

The genetic risk score was designed to identify those with incident CHD and those with a prevalent end-organ disease (previous myocardial infarction, stroke and heart failure) upon inclusion in the MDCS were therefore excluded, which resulted in 23000 cases remaining. By this selection, the original 378 cases of cardiac arrest from Paper III were reduced to 252 cases, which translated to 126 exclusions in our study. A GRS was obtained for all the 252 cases of cardiac arrest.

The total number of cases was then subdivided depending on cardiac or non-cardiac aetiology. The GRS was analysed crude in a univariate analysis and further divided into quintiles. Groups of low (Q1), moderate (Q2-4) and high (Q5) were created and related to the outcome of incident cardiac arrest depending on cardiac or non-cardiac aetiology. For those patients with an arrest of cardiac aetiology, we constructed a multivariate model in which we adjusted the genetic risk score for cardiovascular risk factors that previously had been shown to be associated with the outcome [183] such as age, male sex, smoking, Apolipoprotein A1 (ApoA1), Apolipoprotein B (ApoB), diabetes mellitus, hypertension and obesity. Based on these results, a composite score of the risk of incident cardiac arrest was created. It was divided into deciles and further divided into groups of low (D1-3), moderate (D4-9) and high risk (D10). The composite score was then related to the outcome of incident cardiac arrest.

Ethical approval

All participants in MDC provided a written consent. The Regional Ethical Review Board in Lund, Sweden approved all studies.

Laboratory analyses (Papers III and IV)

Blood samples were collected from MDCS participants at baseline and serum and plasma was separated within one hour and stored at -80 °C. Quest Diagnostics (San Juan Capistrano, CA) performed the measurements of serum concentrations of ApoA1 and ApoB. These were blinded to case-control status and used an immunonephelometric assay run on the Siemens BNII (Siemens, Newark, DE). The inter-assay variability was < 4.0% for both ApoA1 and ApoB.

A multiplex method that combined polymerase chain reaction (PCR), allele-specific oligonucleotide ligation assays, and hybridization to oligonucleotides coupled to Luminex® 100TM xMAPTM microspheres (Luminex, Austin, TX) was used to determine the genotypes of the MDC participants [184]. Genotypes were initially called by an automated clustering algorithm. The genotype clusters of each SNP were then visually inspected by an operator who was blinded to the participant's event status. Outlier genotypes were manually called. This process resulted in genotypes with better than 99% concordance with genotyping by a second method (real-time allele-specific PCR)[184].

Statistical analyses

All analyses were performed using SPSS statistical software version 21.0 for Windows (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.). For normally distributed continuous variables, mean and standard deviation (SD) were used as descriptive measures, whereas median and interquartile range (IQR) was used for skewed distributions. Normality was visually assessed using histograms. Students T-test or Mann-Whitney test was used to compare group means (medians) of continuous variables and Chi-square test or Fischer's exact test were used for comparison of group frequencies. Variables, which displayed significant differences between groups, were then analysed using either Cox proportional hazards model (Papers III and IV) or logistic regression (Papers I, II, III). A two-sided P-value <0.05 was considered as nominally statistically significant. Sensitivity, specificity and AUROC-curves were calculated for PAM-, PAR- (Paper I) and GO-FAR scores (Paper II). Kaplan Meier plots was used for survival analysis (Paper IV). Interaction analyses were performed in Paper III.

Results

Paper I

A total number of 287 cases of IHCA were identified during 2007-2010. Mean age was 70.1 years (SD 14.8) and 61.3% were of male gender. Overall survival to discharge was 20.2%. Basic characteristics of the cohort are presented in table 5.

Table 5

Basic characteristics, univariate analysis

Variable	Survival to discharge	Non-survival to discharge	*p*
No of patients (%)	n=58 (20.2)	n=229 (79.8)	NA
Female sex (%)	n=19 (32.8)	n=92 (40.2)	0.300b
Mean Age (years)	65.4 (SD 15.0)	71.3 (SD 14.5)	0.007a
Initial cardiac rhythm (%)			
VF	n=29 (50.0)	n=26 (11.4)	<0.001b
VT	n=10 (17.2)	n=15 (6.6)	0.010b
PEA	n=7 (12.1)	n=68 (29.7)	0.006b
AS	n=12 (20.7)	n=120 (52.4)	<0.001b
Cardiac monitoring (%)	n=42 (72.4)	n=110 (48.0)	0.001b

NA= Not available, a=Independent T-test, b=Chi-square, VF=Ventricular fibrillation, VT=Ventricular tachycardia, PEA=Pulseless electrical activity, AS=Asystole

Pre-arrest factors with <20% missing values from table 4 were analysed to detect group differences. Variables with a statistically significant association with survival are represented in table 6.

Table 6
Pre-arrest factors compared to survival, univariate analysis

Variable	Survival to discharge	Non-survival to discharge	p
Heart rate (per bpm) *	78.9 (SD 26.6)	89.8 (SD 26.7)	0.010a
Pulse oxymetry (%) *	93.4 (SD 11.1)a	92.7 (SD 7.0)a	0.031c
P-Na (mmol/L) *	138.5 (SD 4.6)	136.7 (SD 5.0)	0.031a
STEMI (%) *	n=14 (24.1)	n=24 (10.5)	0.006b
Independent ADL (%) *	n=54 (93.1)	n=177 (77.3)	0.007b
Malignancy (%) *	n=1 (1.7)	n=44 (19.2)	0.001b

* = Missing values<20%, a=Independent T-test, b=Chi-square, c=Mann Whitney, ADL=Activities of Daily Life, STEMI=ST-elevation myocardial infarction

Odds ratio (OR) (95% CI) for failure to survive was 6.49 (1.50-28.19) (p=0.013) for PAM>6 and 3.88 (1.95-7.73) (p<0.001) for PAR>4. Specificity increased along with increasing score but sensitivity decreased. The area under the receiver operator characteristic (AUROC) curve for PAM was 0.60 (0.53-0.67) (p=0.018) and for PAR 0.72 (0.65-0.79) (p<0.001). The distribution of PAM- and PAR-scores compared to survival are shown in Paper I (Fig 1 and Fig 2).

Comorbidities and other clinical variables compared to failure to survive to discharge are presented in table 7 and adjusted for sex and age.

Table 7
Significant variables in relation to failure to survive to discharge in uni- and multivariate logistic regression analysis

	Crude		Adjusted for sex and age	
Variable	OR (95% CI)	p	OR (95% CI)	p

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Age (years)	1.025 (1.006-1.044)	0.009	1.025 (1.006-1.044)	0.010
Non shockable vs shockable cardiac rhythm	9.41 (4.94-17.92)	<0.001	9.86 (5.08-19.12)	<0.001
Cardiac monitoring	0.35 (0.19-0.66)	0.001	0.38 (0.20-0.72)	0.003
Heart rate (per bpm)	1.019 (1.004-1.034)	0.010	1.024 (1.009-1.040)	0.002
Pulse oxymetry (%)	0.99 (0.94-1.03)	0.599		
P-Na (mmol/L)	0.92 (0.86-0.99)	0.032	0.92 (0.85-0.99)	0.023
STEMI	0.37 (0.18-0.77)	0.008	0.32 (0.15-0.69)	0.004
Independent ADL	0.25 (0.09-0.73)	0.011	0.27 (0.09-0.78)	0.016
Malignancy	13.56 (1.83-100.60)	0.011	13.86 (1.86-103.46)	0.010

Paper II

Two-hundred-and-eighty-seven cases of IHCA between 2007 and 2010 were analysed. A majority were male and mean age was 70.1 years (SD 14.8). Survival to discharge with CPC=1 was 15.7%. Basic characteristics of the cohort are presented in table 5.

GO-FAR score compared to survival with CPC=1 had an OR of 0.86 (0.82-0.90) (p<0.001) per additional point. The AUROC for the GO-FAR score was 0.85 (0.78-0.91) (p<0.001).

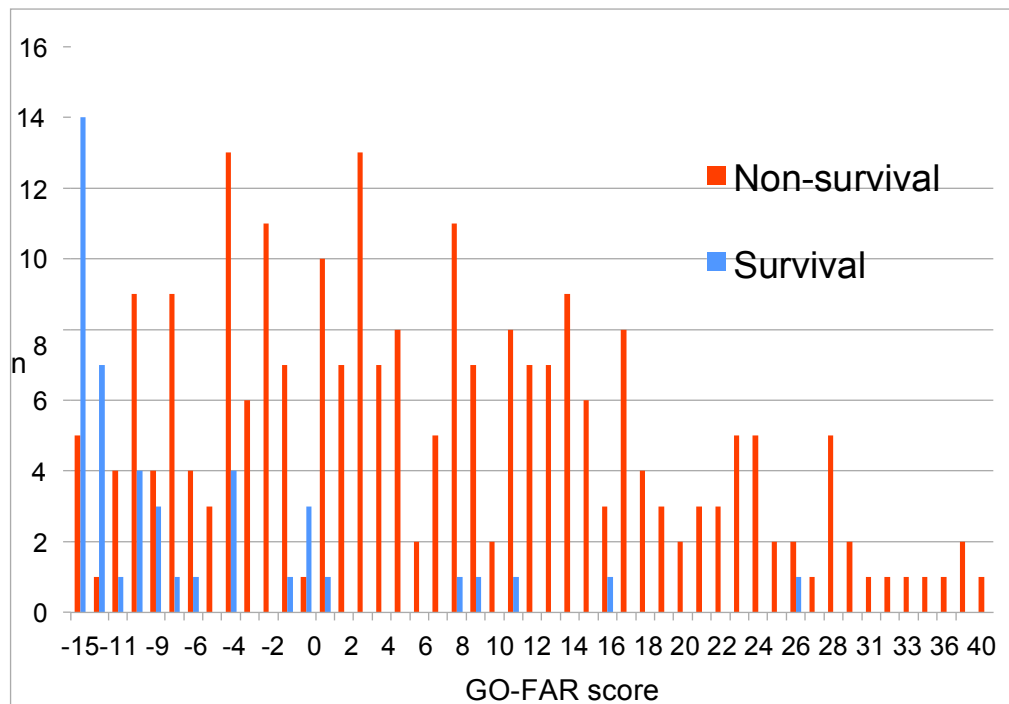The distribution of the GO-FAR score compared to survival is shown in figure 5.

Figure 5. Distribution of GO-FAR score compared to survival

The frequencies of survival and their relation to different risk groups are demonstrated in table 8.

Table 8
Rates of survival to discharge with CPC=1 by GO-FAR risk group

GO-FAR Score (points)	Risk Group	Patients in risk group (%)	Survivors / total in risk group	Survivors (%) (95% CI)
>= 24	Very low[*]	9.1	1/26	3.8 (0.0 – 11)
14 to 23	Low[*]	16.4	1/47	2.1 (0.0 – 6.3)
>= 14	Very low or low[*]	25.5	2/73	2.8 (0.0 – 6.7)
-5 to 13	Average[*]	51.2	12/147	8.2 (3.7 – 13)
-15 to -6	Above average[*]	23.3	31/67	46 (34 – 58)
*=probablity of survival to discharge with CPC=1				

Paper III

The MDCS included 30 447 patients. Mean age at the time of screening was 58.0 years (SD 7.6) and a majority were female (60.2%). Basic characteristics of the cohort are presented in table 9.

Table 9
Basic characteristics, univariate analysis

Variable	Control group (n=30 069), n (%)	Arrest of cardiac origin (n=272), n (%)		Arrest of non-cardiac origin (n=106), n (%)	
			p		*p*
Male sex	11 872 (39.5)	194 (71.3)	<0.001a	55 (51.9)	0.011a
Age (years)	57.6 (12.9)	62.3 (9.4)	<0.001b	62.6 (9.6)	<0.001b
Finished elementary school or higher (yes/no)	27 905 (99.1)	254 (98.8)	0.582a	97 (100)	0.360a
Living alone (yes/no)	6 965 (24.7)	43 (16.7)	0.003a	17 (17.5)	0.105a
Smoking (yes/no)	7 961 (28.2)	93 (36.0)	0.006a	33 (34.0)	0.211a
Obesity (yes/no)	4 167 (13.9)	47 (17.3)	0.110a	31 (29.2)	<0.001a
ApoA1 (mg/L)	156.8 (SD 28.2)	146.1 (SD 26.5)	<0.001c	152.5 (SD 25.2)	0.149c
ApoB (mg/L)	107.1 (SD 26.1)	117.6 (SD 25.1)	<0.001c	108.2 (SD 21.6)	0.701c
Systolic BP (mm/Hg)	141.0 (SD 20.0)	150.2 (SD 21.0)	<0.001c	149.1 (SD 21.6)	0.145c
Antihypertensive	4 558 (15.2)	68 (25.0)	<0.001a	35 (33.0)	<0.001a

treatment (yes/no)					
Lipid lowering treatment (yes/no)	891 (3.0)	23 (8.5)	<0.001a	5 (4.7)	0.306a
Antidiabetic treatment (yes/no)	476 (1.6)	19 (7.0)	<0.001a	6 (5.7)	0.001a
Antiplatelet drug therapy (yes/no)	721 (2.6)	16 (6.3)	<0.001a	4 (4.0)	0.331a
History of prevalent CAD (yes/no)	732 (2.4)	33 (12.1)	<0.001a	8 (7.5)	0,001a
History of prevalent stroke (yes/no)	315 (1.0)	12 (4.4)	<0.001a	6 (5.7)	<0.001a
History of prevalent heart failure (yes/no)	83 (0.3)	3 (1.1)	0.043d	1 (0.9)	0.262d
History of prevalent atrial fibrillation or flutter (yes/no)	306 (1.0)	5 (1.8)	0.181a	1 (0.9)	1.00d
History of prevalent diabetes mellitus (yes/no)	1 293 (4.3)	37 (13.6)	<0.001a	10 (9.4)	0.011a

a=Chi-square, b=Mann-Whitney, c=Students T-test, d=Fischer's exact test, d=median (interquartile range)

BP=blood pressure, CAD=Coronary artery disease

During a mean follow-up time of 17.6 years (SD 4.6), 378 patients suffered a cardiac arrest. Of these 65.9% were males and mean age was 74.6 years (SD 7.1). Overall survival to discharge was 17.2%. The cause of arrest was determined to be of cardiac aetiology in 68.7% of the cases.

Baseline characteristics were related to incident cardiac arrest and in table 10 the different multivariate risk models for arrest of cardiac or non-cardiac aetiology are presented.

Table 10

Final multivariate predictors for arrests of cardiac and non-cardiac aetology

Variable	Cardiac aetiology		
	HR	CI (95%)	*p*
Female sex	0.44	0.31-0.61	<0.001
Age (years)	1.08	1.05-1.11	<0.001
Living alone (yes/no)	0.65	0.44-0.97	0.034
Smoking (yes/no)	2.01	1.50-2.70	<0.001
ApoA1 (mg/L)	0.99	0.98-1.00	0.001
ApoB (mg/L)	1.01	1.01-1.02	<0.001
Antihypertensive treatment (yes/no)	1.35	0.96-1.89	0.081
History of stroke (yes/no)	1.60	1.31-1.95	<0.001
History of CAD (yes/no)	3.08	1.92-4.94	<0.001
History of heart failure (yes/no)	2.50	1.15-5.43	0.021
History of diabetes mellitus (yes/no)	2.24	1.44-3.48	<0.001

	Non-cardiac aetiology		
	HR	CI (95%)	*p*
Female sex	0.66	0.42-1.04	0.073
Age (years)	1.09	1.05-1.14	<0.001
Smoking (yes/no)	2.43	1.53-3.86	<0.001
Antihypertensive treatment (yes/no)	2.00	1.21-3.30	0.007
Obesity (yes/no)	2.00	1.18-3.41	0.01

HR=Hazard ratio, CAD=Coronary artery disease

The variable "Living alone" was significantly associated with a lower risk of cardiac arrest of cardiac aetiology in the univariate analysis. Subsequent sub analyses showed this association to be related to gender; women tended to live alone more often than men (28.3%, versus 18.9%, p<0.001). Interaction analysis between the variable "Living alone" against sex and gender showed a non-

significant interaction with gender (p=0.150) but a significant interaction with age (p=0.008). Stratification of the age-variable into above or below the median age and further analysis by means of Cox regression showed that patients older than 58 years explained the interaction (age<58 years: HR 1.29 CI 0.76-2.19, p=0.34, age>58 years: HR 0.45, CI 0.28-0.72, p=0.001).

Paper IV

This study included 23300 patients. Two-hundred-fifty-two patients suffered a cardiac arrest during the follow up of 18.9 years (SD 4.4). Of these, 181 cases were determined to be of cardiac aetiology and 71 of non-cardiac aetiology. Mean age at the time of screening was 58.0 years (SD 7.7) and a majority were female (62.2%). The basic characteristics of the cohort are presented in table 11.

Table 11
Basic characteristics, univariate analysis

Variable	Control group, (n=23048), n (%)	Arrest of cardiac origin, (n=181), n (%)		Arrest of non-cardiac origin, (n=71), n (%)	
			p		p
Male sex	8646 (37.5)	22 (67.4)	<0.001a	36 (50.7)	0.025a
Age (years)e	57.4 (13.1)	61.2 (9.7)	<0.001b	62.9 (9.8)	<0.001b
Finished elementary school or higher (yes/no)	22824 (99.3)	178 (98.9)	0.543a	71 (100)	0.470a
Living alone (yes/no)	5659 (24.6)	34 (18.8)	0.073a	12 (16.9)	0.136a
Smoking (yes/no)	6418 (27.8)	71 (39.2)	0.001a	26 (36.6)	0.104a
Obesity (yes/no)	2995 (13.0)	36 (19.9)	0.007a	22 (31.0)	<0.001a
ApoA1 (mg/L)	157.2 (SD 28.0)	146.7 (SD 28.1)	<0.001c	150.8 (SD 25.1)	0.055c
ApoB (mg/L)	106.7 (SD 26.0)	118.0 (SD 26.9)	<0.001c	106.1 (SD 21.5)	0.833c
Systolic BP (mm/Hg)	140.9 (SD 20.1)	150.3 (SD 20.7)	<0.001c	146.1 (SD 21.0)	0.032c
Diastolic BP (mm/Hg)	85.4 (SD 10.0)	89.9 (SD 10.8)	<0.001c	87.5 (SD 11.0)	0.085c

Antihypertensive treatment (yes/no)	3425 (14.9)	39 (21.5)	0.013a	23 (32.4)	<0.001a
Lipid lowering treatment (yes/no)	499 (2.2)	9 (5.0)	0.010a	3 (4.2)	0.204d
Antidiabetic treatment (yes/no)	348 (1.5)	11 (6.1)	<0.001a	4 (5.6)	0.025d
Antiplatelet drug therapy (yes/no)	346 (1.5)	4 (2.2)	0.356d	2 (2.8)	0.291d
History of prevalent atrial fibrillation or flutter (yes/no)	196 (0.9)	0 (0)	0.411d	0 (0)	1.00d
History of prevalent diabetes mellitus (yes/no)	892 (3.9)	19 (10.5)	<0.001a	5 (7.0)	0.177a

a=Chi-square, b=Mann-Whitney, c=Students T-test, d=Fischer's exact test, e=median (interquartile range), BP=blood pressure. No cases of prevalent heart failure, prevalent cerebrovascular disease or prevalent coronary heart disease included

A univariate cox regression analysis of the GRS yielded a HR=1.25 {(95% CI 1.11-1.41) (P<0.001)} in relation to all cardiac arrests (cardiac and non-cardiac aetiology). The corresponding HR for cardiac arrest of cardiac aetiology was 1.33 {(95% CI 1.15-1.53) (P<0.001)} and for non-cardiac aetiology 1.08 {(95% CI 0.86-1.36) (P=0.519)}.

A multivariate model was then created in which the GRS was represented as low-, medium- and high-risk and compared to incident cardiac arrest of cardiac (A) and non-cardiac aetiology (B) (table 12).

Table 12
Cox regression analysis of incident cardiac arrest

A. Cardiac origin (n=181)			
Variable	**HR**	**_p_**	**CI (95%)**
Age (years)	1.08	<0.001	1.06-1.10
Male sex (yes/no)	2.85	<0.001	2.05-3.96
Smoking (yes/no)	2.20	<0.001	1.62-2.99
Diabetes Mellitus (yes/no)	2.29	0.001	1.41-3.70
Hypertension (yes/no)	1.51	0.027	1.05-2.17
Apo A1 (mg/L)	0.99	0.023	0,99-1.00

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Apo B (mg/L)	1.01	0.001	1.00-1,02
Obesity (yes/no)	1.40	0.077	0.96-2.05
GRS-CHD low		0.001	
GRS-CHD medium	1.71	0.025	1.07-2.73
GRS-CHD high	2.53	<0.001	1.52-4.19

B. Non-cardiac origin (n=71)

Variable	HR	*p*	CI (95%)
Age (years)	1.11	<0.001	1.07-1.15
Male sex (yes/no)	1.56	0.083	0.94-2.58
Smoking (yes/no)	2.34	0.001	1.42-3.85
Diabetes Mellitus (yes/no)	1.38	0.489	0.55-3.47
Hypertension (yes/no)	1.27	0.408	0.72-2.24
Apo A1 (mg/dL)	1.00	0.346	0.99-1.01
Apo B (mg/dL)	0,99	0.054	0.98-1.00
Obesity (yes/no)	2.96	<0.001	1.75-5.02
GRS-CHD low		0.841	
GRS-CHD medium	1.15	0.670	0.62-2.13
GRS-CHD high	1.25	0.559	0.59-2.63

Next a composite score was created based on those variables showing significance in table 12 A. Presence of dichotomous risk factors and presence of above the median value of continuous risk factors yielded 1 point. Low, medium and high genetic risk yielded 0, 0.5 and 1 point respectively as shown in table 13.

Table 13
Composite score, risk of incident cardiac arrest, 0-8 points

Male sex (yes/no)		1
Age > median (57.5 years)		1
GRS		
	low	0
	medium	0.5
	high	1
ApoA1 < median (157.2)		1
ApoB > median (106.8)		1

Diabetes (yes/no)	1
Hypertension (yes/no)	1
Smoking (yes/no)	1

When analysed in Cox regression, each SD increment of the composite score conferred a HR of 2.81 {(95% CI 2.38-3.31) (P<0.001)}. Compared with the low risk group of the composite score, subjects in the intermediate risk group of the composite score had a HR of 24.55 {(95% CI 6.07-99.26) (P<0.001)} and subjects in the high risk group of the composite score had a HR of 82.19 {(95% CI 20.07-336.69) (P<0.001)} for developing cardiac arrest. The corresponding Kaplan Meier curve for the low-, moderate- and high risk groups of the composite score is illustrated in figure 6.
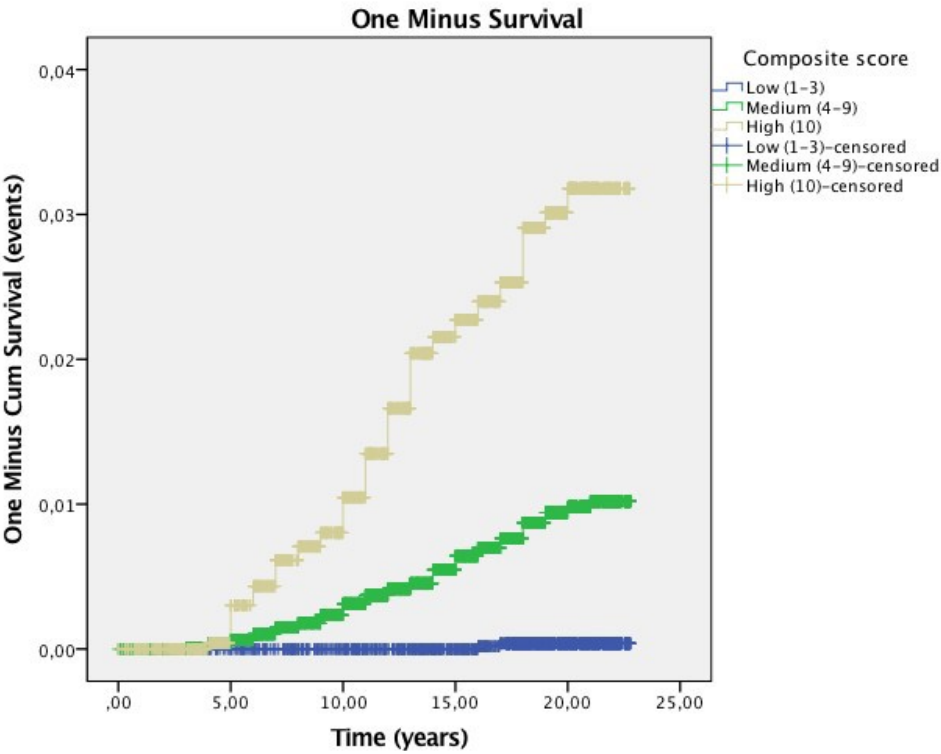

Figure 6. Kaplan Meier Curve for low-, moderate- and high risk groups of the composite score

Discussion

Cardiac arrest is a life-threatening condition against which CPR and defibrillation is the only effective treatment. Information about this condition and its treatment among the general public has improved greatly during the last decades. We now see both bystander CPR and the use of public AEDs, which has improved the outcome of OHCA [25, 185]. A lot of efforts have been put into education and optimization of the pre-hospital management. The post-resuscitation care has also improved markedly and the vast majority of those who survive to discharge from the hospital do so with a CPC-score of 1-2 [135].

Concerning IHCA, there have also been considerable improvements. Most hospitals now have emergency teams that are dispatched when a patient is found in cardiac arrest. The time to defibrillation and quality of CPR has improved as well as survival to discharge [135].

Despite these advances in the last decades, there are still gaps in the knowledge about pre-arrest assessment of patients – who will benefit from CPR and who will not? In the latest guidelines from the Swedish Council of CPR, only prevalent diabetes is mentioned as a pre-arrest factor that has been shown to be associated with a poor outcome [135]. Is CPR in some cases to be regarded to be futile and could it potentially harm the patient? CPR is sometimes complicated by neurological injury, painful rib fractures, pneumonia and prolonged mechanical ventilation. About 1/3 of the survivors choose not to undergo CPR again if necessary [186, 187]. Thus, an individual and careful assessment of risk versus benefit should be performed when discussing future CPR strategies. It would also be beneficial to physicians, patients and their relatives, if more and better information about CPR and its possible complications was directed towards the public since the awareness of this matter still is insufficient. Moreover, it is my personal opinion that, physicians to a larger extent should discuss CPR, chances of survival and possible complications as well as other end-of-life strategies with their patients.

There is also scarce scientific work performed in the area of risk assessment of future cardiac arrest among the general population. Which risk factors are the most important? Does the risk factor-pattern differ with regard to the aetiology of the arrest? How could the risk assessment be improved? Could genetic analyses individualize the risk assessment and in the long run the preventive measures?

Paper I

In paper I we aimed to investigate whether PAM- and PAR-scores were accurate enough to be relied on for pre-arrest assessment in the hospital setting. We also aimed to see if new clinical variables, that were not included in the scores, could add information. Previous studies based on these scores were made long ago with markedly lower survival rates than current ones [103]. The PAM- and PAR-scores were unfortunately not accurate enough to estimate who would benefit from CPR and who would not, although cut-off values of PAM>5 and PAR>5 were associated with a specificity above 90% for failure to survive an IHCA. However, our finding of hyponatremia and elevated heart rate upon admission being associated with poor survival was novel in the setting of IHCA and requires further replication. Hyponatremia has previously been linked to both overall mortality [188] as well as increased mortality in patients with heart failure [189], although no casual connection has been established. Tachycardia has been shown to be associated with increased mortality in chronic haemodialysis patients [190] and also in those with sepsis [191]. Several studies have shown increased cardiovascular morbidity in patients with elevated heart rate [192-194] and in the Framingham study an association with sudden death was also observed [195]. The causality of these findings remains unclear. The fact that presence of STEMI is associated with improved survival of IHCA has previously been observed [103] and could be validated in our study. An increased frequency of cardiac monitoring, a higher proportion of shockable rhythm in the setting of acute myocardial ischemia [101] as well as a potentially reversing treatment in the form of revascularisation could be speculated to explain this finding.

Limitations of this study were numeral; missing values, both laboratory values and vital parameters in the most ill patients, constituted a problem. Moreover, the relatively small number of patients included could potentially explain why severe acute conditions such as septicaemia, acute stroke, acute renal failure and acute heart failure as well as chronic comorbidities did not yield significant results concerning failure to survive although this is often observed in clinical practice. Data of current medications were unfortunately not obtained in this study. The use of beta-blockers could potentially affect the result of elevated heart rate being associated with a poor outcome, as the use of beta-blockers previously has been associated with improved survival in IHCA in a study by Gonzalez et al [107]. Also, there probably was an effect of selection bias present in this study since the most severely ill patients had DNR-orders and thus were not included in the study.

Concerning the finding of malignancy being strongly associated with failure to survive with an OR=13.86 {(95% CI 1.86-103.46) (P=0.010)}, some selection bias could potentially be present here as well. Cases of cardiac arrest in which CPR is

initiated could be prematurely interrupted if information about an advanced malignant condition is revealed during the resuscitation. Notes about prematurely interrupted CPR was not included in the data available and could thus not be assessed. One could speculate that this could be assessed retrospectively if the total duration of the CPR would be compared between CPR in patients with and without malignancy, the total duration of CPR could then possibly be shown to be significantly shorter in cases of an underlying malignant condition. The total time of resuscitation was unfortunately not available in the current data.

Paper II

In this paper we aimed to investigate whether the newly devised GO-FAR score would be accurate enough to be used as an instrument of pre-arrest assessment concerning IHCA. The original study was performed on 51 240 patients in USA and since the demographics and overall survival differed between USA and Sweden, it was necessary to perform a smaller validation study locally. The GO-FAR score performed well reaching an AUROC=0.85, consistent with very good discrimination. Important demographic differences were noted in the Swedish cohort such as an older population, a larger proportion of male gender and ethnically more homogenous. Better overall survival rates CPC-levels upon discharge were also observed compared to the original study, which is aligned with current Swedish data [135].

Limitations included difficulties assessing CPC upon admission as well as the relatively low sample size of patients. In the groups of "very low-" and "low probability of survival", there was each a single survivor. Both survivors were under the age of 40, which calls for caution using the score on younger patients. Survival was somewhat higher in the group of "very low probability of survival" compared to the group of "low probability of survival" (3.8% vs. 2.1%). This is probably due to the low sample size in this study. Both groups had one survivor each as mentioned above. When combining the groups of "very low-" and "low probability of survival", only 2/73 patients survived (2.8%, 95% CI 0.0-6.7). The CI of this data included the CI of the same group from the original study (1.6%, 95% CI 1.4-1.8). Although one would prefer a prospective study design for the validation of the score, this would be practically very difficult to put into practice. Tens of thousands of patients would be required to obtain the sufficient number of events, given that IHCA is fairly rare event.

Also, the GO-FAR score is not applicable for those patients with a chronic condition rendering them a CPC-level<1. These patients could never achieve the investigated outcome of survival with CPC=1. The score can therefore formally only be used in patients with an acute reduction in CPC-level due to disease. However, it is reasonably to believe that the score could be extrapolated to those with a chronic CPC-level<1 since the susceptibility to further brain injury would be increased in those with marked reduction in cognitive and neurological capacity.

Recently, new data emerged in the area of pre-arrest assessment. In a study from 2016, a well-known score named Age-combined Charlson Co-morbidity Index (ACCI) was tested on IHCA [196]. Patients were divided into groups of "low burden", "moderate burden" and "high burden" of age-combined co-morbidities. Survival defined as 30-day survival with CPC 1-2 for the different groups, was 47%, 10% and 5% respectively. These results are fairly similar to those of the GO-FAR score with 46%, 8.2% and 2.8% for the respective groups of "above average-", "average-" and "very low or low probability of survival". No data of AU-ROC was presented in the study and the number of patients was low (n=174). Moreover, new scoring systems such as The Pittsburg Cardiac Arrest Category (PCAC) score [197] and Cardiac Arrest Survival Post-resuscitation In-hospital (CASPRI) risk score [198] show promising results but are unfortunately focused only on predicting survival after successful resuscitation rather than pre-arrest assessment.

Finally, the fact that the outcome of the GO-FAR score is specified to CPC=1, could provide difficulties generalising the score since some patients would accept CPC=2 or even CPC=3 as a fair outcome. This emphasizes the importance of discussing CPR and the possibilities of survival with the patients as well as their attitude towards possible cognitive and neurological disabilities post-arrest.

Paper III

After studying the highly selected group of patients admitted to hospital and suffering an IHCA, focus was redirected towards younger and healthier subjects. Our main interests in this study were modifiable risk factors and since the aetiology of cardiac arrest differs, the hypothesis was that the risk factors also differed depending on the aetiology of the arrest. Our aim in this study was thus to assess the risk profile of future cardiac arrest in the general population and to investigate whether this risk profile differed depending on cardiac or non-cardiac aetiology of the arrest.

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A clear difference was found in midlife risk factor pattern; cardiac arrest of cardiac aetiology was dominated by traditional cardiovascular risk factors whereas those with an arrest of non-cardiac aetiology to a larger extent were smokers and suffered from hypertension and obesity. These findings emphasize the importance of aggressive preventive measures against cardiovascular risk factors as well as better population strategies and individual patients' efforts to prevent and treat obesity which we know is a growing global problem [199].

At the start of the MDC-study, only about 20% of the cohort had a foreign background, coming mainly from Finland, Denmark, Germany, former Yugoslavia, Poland and Hungary [178]. The demographics have since then changed markedly towards increased heterogeneity and in 2015 the proportion of foreign background among the inhabitants in Malmö was about 43% [200]. This difference could potentially hamper the generalizability of our results.

The categorization of cardiac and non-cardiac aetiology is somewhat complex, since most patients lack an autopsy confirming the cause of death. The autopsy rate has decreased in Sweden from 80% in the late 70's to 39% in the late 80's [201]. In 2013 the rate had declined further to about 11% of the total number of diseased in Sweden [202]. Using the different definitions explained in the Methods section of *Paper III*, we found that 68.7% of the cases of cardiac arrest were of cardiac aetiology. This finding is aligned with previous reports [25, 27], although lower rates of cardiac aetiology have been reported concerning IHCA [203]. Moreover, our classification of aetiology is supported by the results in *Paper IV*, in which the group of cardiac aetiology is clearly associated with the GRS, while the group of non-cardiac aetiology is not.

Other limitations of this study is the fact that the participants of the cohort generally are healthier than non-participants. This is seen in a study from 2001 [177] in which cancer incidence and total mortality are shown to be lower among the participants the MDC cohort. A possible source of selection bias is potentially missed cases of cardiac arrest in the cohort between 1991 and 1999. This is due to the fact that inclusion into the MDC-study took place 1991-1996 and the local cardiac arrest registry was not initiated until 1999. If a patient was found diseased and had a, by autopsy, determined cardiac death, it would not register as an event in our study. The subject would be censored from follow-up from the time of death. The same is true for non-cardiac causes such as ruptured aortic aneurysm or pulmonary embolism leading to a cardiac arrest of non-cardiac aetiology. These potentially missed cases could have been patients of the highest risk of incident cardiac arrest. Patients with other mortal conditions such as malignancies would also have been censored, thus constituting a competing risk. This is worth considering and could possibly weaken the associations between cardiac arrest and

its risk factors. However, the potentially missed cases are believed to be in negligible numbers to affect our overall results.

Furthermore, the study design of registration of data upon inclusion followed by a long follow-up time without further clinical examinations could be criticized. Risk factors upon inclusion could potentially change during follow-up. A better design would be to have repeated clinical examinations at a regular basis as the study progresses. This way, the risk factor profile of the individual patient would be accurate and up to date. To which extent this would affect our data is difficult to assess. However, since the mean age upon inclusion was fairly high at 58 years, several risk factors such as hypertension, smoking, diabetes and obesity, were probably already present upon inclusion and would not change prospectively.

Paper IV

In the fourth and final paper we aimed to investigate whether a GRS for CHD could predict incident cardiac arrest of cardiac aetiology in a cohort free from end-organ damage such as heart failure, cardiovascular- and cerebrovascular disease. The GRS turned out to be one of the strongest risk factors, surpassed only by male sex in a multivariate model including traditional cardiovascular risk factors. Moreover, a composite score based on traditional risk factors together with low-, medium- and high genetic risk was strongly associated with incident cardiac arrest of cardiac aetiology when comparing the highest decile against the low risk group. These findings are novel and encouraging towards a better and individualised risk assessment of future cardiac arrest. As for now, one could only speculate how this could be applied clinically; those patients with low- or medium cardiovascular risk but high genetic risk should perhaps have other targets than current ones regarding optimal blood pressure and lipid levels? Also, those with high cardiovascular risk and high genetic risk should perhaps have even lower target levels? The group with the highest risk could potentially benefit from an implantable cardiac device.

As always when dealing with genetic data that could change the risk profile of a certain individual, there are ethical aspects that should be considered. Some patients are likely to not be interested in their genetic risk and repercussions concerning health insurance policies could possibly constitute a problem for some.

The limitations in this study are in part identical to the ones in paper III such as a demographic change in the city of Malmö since the inclusion and participants being more health-oriented than non-participants. Moreover, the lack of data concerning electrolytes, renal function, EKG and echocardiography are also a

limitation. Finally, the relatively small sample size of events could reduce the generalizability of the results.

Future perspectives

Many questions remain as to how an optimal pre-arrest assessment could be performed. There are constantly new laboratory developments being made and in the future hopefully high sensitive laboratory parameters combined with current variables could assist in determining who is at risk of cardiac arrest and the prognosis of survival.

The survival rates of IHCA have improved greatly during the last years [66, 135] and the reasons for this are largely unknown. It has been speculated that this change originates in a better selection of patients in whom CPR is initiated, but this has not to my knowledge been further studied.

We know that survival of IHCA is greater in those patients that are subjects of cardiac monitoring [110, 111, 135] and lower for those admitted to medical wards [135]. Perhaps smaller and cheaper portable devices that would signal lethal arrhythmia would be accessible ahead? This could potentially improve survival in those patients at medical wards without a DNR-order.

Finally, individualised risk assessments and treatments are a part of the future and a necessary development towards an optimised medical care and prevention of disease. If our genetic data and composite risk score could be improved with addition of EKG-criteria and more laboratory parameters as described in a study by Deo et al [204], the accuracy of the prediction of risk of future cardiac arrest could possibly be enhanced even further.

Conclusions

- The PAM- and PAR-scores are not sufficiently accurate in prediction of survival of IHCA. Hyponatremia and elevated heart rate upon admission were associated with poor survival and could potentially represent new tools for risk stratification

- The GO-FAR score is an accurate instrument in prediction of survival with CPC=1 in cases of IHCA. The GO-FAR score performs well even when tested on a smaller population with different demographics than originally investigated

- Midlife risk factors for incident cardiac arrest differ depending on cardiac- or non-cardiac aetiology of the arrest. In addition to control of classical cardiovascular risk factors, an intensified prevention of obesity may reduce the risk of future cardiac arrest of non-cardiac aetiology

- Genetic risk of CHD is strongly and independently associated with incident cardiac arrest of cardiac aetiology. A composite risk score comprised of genetic risk together with classical cardiovascular risk factors may identify individuals of high risk of future cardiac arrest, among whom preventive measures should be intensified

Populärvetenskaplig sammanfattning

Bakgrund och målsättning

Plötsligt hjärtstopp drabbar ca 10 000 individer i Sverige årligen. Överlevnaden har förbättrats under de sista 20 åren och idag överlever ca 1/10 av de som får sitt hjärtstopp utanför sjukhus medan ca 3/10 överlever om hjärtstoppet sker på sjukhus.

Behandling med hjärtlungräddning bestående av hjärtkompressioner, inblåsning av luft samt s.k. defibrillering av hjärtmuskeln är essentiell för överlevnaden. För varje minut som passerar utan hjärtlungräddning minskar överlevnaden med 10 % och efter ca 5 minuter utan behandling börjar hjärnskador att utvecklas relaterat till den syrebrist som uppstår utan effektiv cirkulation och andning. I många fall lyckas man tillfälligt återställa cirkulation och andning med hjälp av hjärtlungräddning men patienterna avlider sedermera p.g.a. de skador de ådragit sig. Vanliga komplikationer till behandlingen med hjärtlungräddning är frakturer på bröstben och revben, lunginflammation, neurologiska och kognitiva skador samt långa perioder med respiratorvård. Över 90 % av de som överlever till utskrivning från sjukhus har dock endast lätta till måttliga neurologiska och kognitiva skador.

Ca 75 % av fallen med hjärtstopp beror på en underliggande hjärtsjukdom medan resterande fall har olika orsaker såsom trauma, akut blödning, andningssvikt eller förgiftning. Lite är för närvarande känt kring vilka riskfaktorer som har störst betydelse för att i framtiden drabbas av ett hjärtstopp.

Den grupp av patienter som får hjärtstopp på sjukhus är speciell eftersom denna grupp i regel är betydligt sjukare i grunden än den grupp som får sitt hjärtstopp utanför sjukhus. Hos de allra sjukaste patienterna väljer man ofta att inte påbörja hjärtlungräddning i händelse av hjärtstopp då behandlingen anses vara utsiktslös eller inte vara till gagn för patienten. Enligt nuvarande lagstiftning och etiska rekommendationer ska ett sådant beslut diskuteras med patient eller anhöriga men är i slutändan ett rent medicinskt beslut. Exakt på vilka medicinska grunder ett sådant beslut fattas varierar mellan sjukhus och även mellan olika läkare. Det saknas för närvarande effektiva och objektiva instrument för att bedöma chansen till överlevnad av ett hjärtstopp hos patienter som är inlagda på sjukhus.

Denna avhandling syftar till att belysa följande problemområden:

1. Hur kan vi bättre bedöma förutsättningarna till överlevnad av hjärtstopp hos patienter som vårdas inneliggande på sjukhus?

2. Hur kan vi bättre bedöma risken för framtida hjärtstopp hos en medelålders och frisk population?

Metod och Resultat

I studie I undersöktes 287 fall av hjärtstopp på sjukhus mellan 2007-2010. Vi testade här två befintliga poängsystem, Pre-Arrest Morbidity score (PAM) och Prognosis After Resuscitation score (PAR), för att försöka uppskatta patienternas chans till överlevnad av hjärtstopp. Poängsystemens träffsäkerhet var överlag låg även om vi kunde observera att enskilda faktorer såsom ålder, cancersjukdom, låg funktionsnivå, lågt saltvärde (hyponatremi) samt hög puls var associerat med en försämrad överlevnad. Om patienterna visade sig få sitt hjärtstopp p.g.a. en akut hjärtinfarkt (ST-höjningsinfarkt, STEMI) visade sig överlevnaden vara bättre än om orsaken var en annan.

I studie II undersöktes samma grupp av patienter som i studie I men med ett nytt poängsystem vid namn Good Outcome Following Attempted Resuscitation (GO-FAR-score). Detta poängsystem syftar till att identifiera de patienter med "väldigt låg-", "låg-", "måttlig-" eller "hög" sannolikhet till överlevnad med endast lätta neurologiska eller kognitiva skador. Vi kunde här visa en betydligt bättre träffsäkerhet än i föregående studie vilket möjliggör en användning av detta poängsystem i den kliniska vardagen.

I studie III övergick vi till att undersöka 30 447 medelålders och väsentligen friska individer i Malmö Kost Cancer-studien avseende förekomst av hjärtstopp under en drygt 18 år lång uppföljningstid. Vi skapade här olika riskprofiler för framtida hjärtstopp beroende på om hjärtstoppet var en konsekvens av underliggande hjärtsjukdom eller inte. Bland de individer som fick hjärtstopp p.g.a. underliggande hjärtsjukdom var stigande ålder, rökning, blodfettsrubbningar tillsammans med förekomst av stroke, kranskärlssjukdom, hjärtsvikt och diabetes tydliga riskfaktorer för framtida hjärtstopp. Bland de individer som fick hjärtstopp utan underliggande hjärtsjukdom var högt blodtryck, rökning och fetma de viktigaste riskfaktorerna. Dessa resultat tydliggör vikten av riktade förebyggande åtgärder för att undvika ett framtida hjärtstopp.

I det sista arbetet, studie IV, använde vi oss av samma studiepopulation som i studie III, men med samtliga individer som hade en känd kranskärlssjukdom, stroke eller hjärtsvikt borträknande. På detta sätt fick vi fram en population

bestående av 23 000 individer utan diagnosticerad hjärt-kärlsjukdom. Hos samtliga av dessa individer fanns en genetisk risk för kranskärlssjukdom kartlagd. Vi använde oss av denna genetiska risk tillsammans med traditionella riskfaktorer för kranskärlssjukdom för att undersöka huruvida man med dessa medel bättre kunde förutsäga risken för framtida hjärtstopp på basen av underliggande hjärtsjukdom. Det visade sig att den genetiska risken var en av de starkaste riskfaktorerna för framtida hjärtstopp, endast manligt kön var statistiskt starkare associerat med detta utfall. Traditionella riskfaktorer såsom rökning, högt blodtryck, blodfettsrubbningar och diabetes var alla svagare riskfaktorer. När vi sedan skapade ett nytt poängsystem bestående av traditionella riskfaktorer tillsammans med låg-, måttlig- och hög genetisk risk kunde vi hos de 10 % med högst risk påvisa en 80-faldigt ökad risk för framtida hjärtstopp. Dessa resultat öppnar upp för en mer individualiserad riskbedömning framöver där genetiken sannolikt kommer att spela en stor roll.

Konklusion

- PAM- och PAR-score är inte tillräckligt träffsäkra för att användas som ett skattningsinstrument för att effektivt bedöma chansen till överlevnad vid hjärtstopp på sjukhus
- Hög ålder, förekomst av cancer, låg funktionsnivå, hyponatremi och hög puls är associerat med en försämrad överlevnad av hjärtstopp på sjukhus. Förekomst av akut hjärtinfarkt (STEMI) är kopplat till en förbättrad överlevnad
- GO-FAR-score är ett tillförlitligt skattningsinstrument för att bedöma chansen till överlevnad av hjärtstopp på sjukhus
- Hos en medelålders population skiljer sig riskfaktorerna för framtida hjärtstopp beroende på orsak till hjärtstoppet. Fetma förefaller vara en stark riskfaktor för framtida hjärtstopp utan underliggande hjärtsjukdom. Dessa resultat kan motivera mer aggressiva förebyggande åtgärder
- Genetisk risk för hjärtkärlsjukdom är en oberoende riskfaktor för framtida hjärtstopp och en starkare sådan än många traditionella kardiovaskulära riskfaktorer
- En ny riskmodell med traditionella kardiovaskulära riskfaktorer tillsammans med hög genetisk risk visar på en 80-faldigt ökad risk för framtida hjärtstopp. En individualiserad riskbedömning och behandling kommer sannolikt bli en realitet i framtiden

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I started my residency at the Department of Internal Medicine in Malmö in 2010. In 2012 I did a small paper together with Linn Kennedy, in which we investigated the attitudes towards DNR-orders at the medical wards at SUS, Malmö. During this work, we discovered the scarse amount of research performed within the area of pre-arrest assessment and the idea of performing a research project focusing on cardiac arrest took form. I had, at this point, virtually no knowledge of the research process and no affiliations within the research community. Many colleagues have helped and supported me during my research and I am thankful towards you all. I would like, however, to direct a special thank you towards the following individuals, without whom, this thesis would never had been written:

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Paper I

Clinical paper

Evaluation of pre-arrest morbidity score and prognosis after resuscitation score and other clinical variables associated with in-hospital cardiac arrest in southern Sweden[u]

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article info

abstract

Objective: To evaluate pre-arrest morbidity score (PAM), prognosis after resuscitation score (PAR) and to identify additional clinical variables associated with survival after in-hospital cardiac arrest (IHCA) treated with cardiopulmonary resuscitation (CPR).

Methods: A retrospective observational study involving all cases of IHCA at Skåne University Hospital Malmö 2007–2010.

Results: Two-hundred-eighty-seven cases of IHCA were identified (61.3% male; mean age 70 years) of whom 20.2% survived until discharge. The odds ratio (95% confidence interval) for death prior to discharge was 6.49 (1.50–28.19) ($p = 0.013$) for PAM > 6 and 3.88 (1.95–7.73) ($p < 0.001$) for PAR > 4. At PAM- and PAR-scores >5, specificity exceeded 90%, while sensitivity was only 20–30%. The odds ratio for in-hospital mortality was 0.38 (0.20–0.72) ($p = 0.003$) for patients with cardiac monitoring, 9.86 (5.08–19.12) ($p < 0.001$) for non-shockable vs shockable rhythm, 0.32 (0.15–0.69) ($p = 0.004$) for presence of ST-elevation myocardial infarction (STEMI), 0.27 (0.09–0.78) ($p = 0.016$) for patients with independent Activities of Daily Life (ADL) and 13.86 (1.86–103.46) ($p = 0.010$) for patients with malignancies. Heart rate (HR) on admission (per bpm) [1.024 (1.009–1.040) ($p = 0.002$)] and sodium plasma concentration on admission (per mmol l^{-1}) [0.92 (0.85–0.99) ($p = 0.023$)] were significantly associated with in-hospital mortality.

Conclusion: PAM- and PAR-scores do not sufficiently discriminate between in-hospital death and survival after IHCA to be used as clinical tools guiding CPR decisions. We confirm that malignancy is associated with increased in-hospital mortality, and cardiac monitoring, shockable rhythm, STEMI and independent ADL, with decreased in-hospital mortality. Interestingly, our results suggest that HR and plasma sodium concentration upon admission may represent new tools for risk stratification.

1. Introduction

According to the Swedish Cardiac Arrest Register (SCAR), 8612 in-hospital cardiac arrests (IHCA) treated with cardiopulmonary resuscitation (CPR) occurred in Sweden between 2005 and 1st of September 2011.[1] Previous reports indicate a survival rate at approximately 15% but it has in the last years improved and among these patients 28% survived to discharge. At Skåne University Hospital, Malmö, where the current study was performed, 402 cases of IHCA occurred 2006-2010 with a survival to discharge-rate ranging from 20 to 22%[2] in subjects who underwent CPR.

In everyday clinical practice, doctors make decisions about initiating or abstaining from CPR. These decisions are based on age, acute and chronic illness of the patient but are also very dependent on the experience of the responsible doctor. The National Board of Health and Welfare in Sweden has no specific advice concerning these decisions and local hospitals have therefore developed their own guidelines. There are few clinical studies on IHCA in the Swedish population, so the local guidelines commonly do not contain any references to scientific studies. The lack of scientific

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Table 1
PAM and PAR-score.

Variable		PAM	PAR
Malignancy		3	
	Metastatic		10
	Non-metastatic		3
Sepsis (on admission)		1	5
Homebound		3	5
Pneumonia (on admission)		3	3
Creatinine			
>220 mmol l⁻¹		3	
>130 mmol l⁻¹			3
Age >70 years			2
Acute MI		1	−2
Hypotension		3	
Heart failure		1	
Angina pectoris		1	
Gallop rhythm		1	
Oliguria		1	
Assisted ventilation		1	
Coma		1	
Acute stroke		1	
Cirrhosis		1	

evidence guiding clinical decision-making of whether initiating or abstaining from CPR, encouraged us to evaluate existing scoring systems associated with survival and non-survival of IHCA, and to identify new clinically useful variables.

2. Methods

We designed a retrospective observational study including all IHCA treated with CPR in patients ≥18 years of age occurring between 2007 and 2010 at Skåne University Hospital, Malmö, Sweden. Cases were identified and analyzed through access to the local cardiac arrest registry and medical record software "Melior". The local ethics committee of Lund University approved the study. At Skåne University Hospital, Malmö, all suspected cardiac arrests result in initiation of an automatic alarm, which reaches the emergency team. After completing the resuscitation, data from every case is registered and sent to the local cardiac arrest registry. A specialized nurse then reviews the data, further data is collected from the medical records and a report is sent to the national cardiac arrest registry. Through access to the local cardiac arrest registry, we recorded a total of 825 cases. These cases were then reviewed by a doctor and of the 825 cases 538 were excluded due to the following reasons: 477 were out-of-hospital cardiac arrests, 8 were duplicates, 9 were patients <18 years of age, 30 were not real cardiac arrests, 6 were cancelled CPR, 6 were suicides and 2 cases were excluded because no information was available in the data base. A total number of 287 cases remained for further analysis.

Ebell et al.[3] and Bowker et al.[4] have evaluated different scoring systems with the goal of being able to predict survivors and non-survivors in patients with IHCA. Several scoring systems have been proposed, among them Pre-arrest Morbidity (PAM, developed by George[5]) and Prognosis after Resuscitation (PAR, developed by Ebell[6]) (Table 1). PAM includes 15 different variables and the score varies from 0 to 25. The variables were chosen based on them being significant predictors of survival in a CPR study by Bedell,[7] others were added based on the authors "clinical intuition".[4] PAR includes only 7 variables and the score varies from -2 to 31. It is based on 14 post-CPR studies that were included in a meta-analysis by Ebell.[6]

Because of their clinical usefulness PAM and PAR were chosen for evaluation. Apart from the variables included in PAM and PAR, a number of variables were added and existing variables in PAM and

PAR were subdivided according to Supplementary Table 1. The variable "Sepsis" was subdivided according to international and local recommendations,[8] the variable "Acute myocardial infarction (MI)" was subdivided according to presence or absence of ST-segment elevation on the diagnostic electrocardiogram. Finally the variable "Homebound" was subdivided into three different variables: "independent Activities of Daily Life (ADL)", "Daily assistance" and "Living in a nursing home". These three categories are routinely used in the local medical records. Variables with missing values in ≥20% were excluded from analysis.

For symmetrically distributed continuous variables, mean and standard deviation (SD) were used as descriptive measures, whereas median and interquartile range (IQR) were used for skewed distributions. Students T-test or Mann–Whitney test was used to compare group means (medians) of continuous variables and Chi-square test was used for comparison of group frequencies. Variables, which displayed significant differences between groups, were then analyzed using logistic regression analyses. A two-sided p-value <0.05 was considered as nominally statistically significant. Area under the receiver operating characteristics (AU-ROC) was calculated for continuous PAM- and PAR-scores. All analyses were performed using SPSS statistical software version 21.0 for Windows (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.).

3. Results

Of the 287 cases, 61.3% were male. The mean age was 70.1 years (SD ±14.8). Survival rate to discharge was 20.2%; among the survivors 67.2% had an initial cardiac rhythm of either ventricular fibrillation (VF) or ventricular tachycardia (VT). Among the non-survivors 82.1% had an initial cardiac rhythm of either pulseless electrical activity (PEA) or asystole (AS). A majority of the survivors to discharge had cardiac monitoring, whereas it was only 48% for the non-survivors.

Fig. 1 shows the distribution of survivors and non-survivors at different PAM-scores. The highest score recorded was 13 and the median value of PAM was 3 (IQR = 1–5). In Fig. 2 the PAR-score is shown, the highest score recorded was 23 and the median value was 3 (IQR = 0–6).

The PAM- and PAR-score treated as continuous variables gave $p = 0.016$ for PAM-score and $p < 0.001$ for PAR-score. Table 2 shows the results of logistic regression analyses with the PAM- and PAR-score dichotomized at increasing cut-off values of the respective score. Both continuous scores were significantly associated with failure to survival to discharge. When the scores were categorized, the highest point estimate of the respective odds ratio was observed for PAM > 6 and PAR > 5. With increasing cut-offs of the two scores, the confidence intervals widened markedly, sensitivity decreased and specificity increased. Data from the AU-ROC showed an area under the curve of 0.601 (0.528–0.674) ($p = 0.018$) for PAM and 0.718 (0.647-0.790) ($p < 0.001$) for PAR.

In Table 3 the basic characteristics are listed including all of the variables from Supplementary Table 1 that turned out to be statistically significant between groups.

In Table 4 the significant variables from Table 3 are listed in relation to failure to survive to discharge with their corresponding odds ratio (OR) and 95% confidence intervals, both represented as crude data and as adjusted for sex and age, except the age-variable which is only adjusted for sex. Pulse oxymetry turned out to be non-significant in the logistic regression analysis. Age was associated with a 2.5% increased risk of non-survival per year. Patients who underwent cardiac monitoring and those who had shockable rhythm had significantly better survival than those who did not.
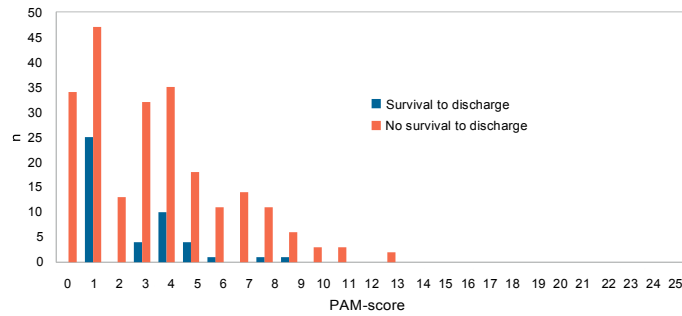
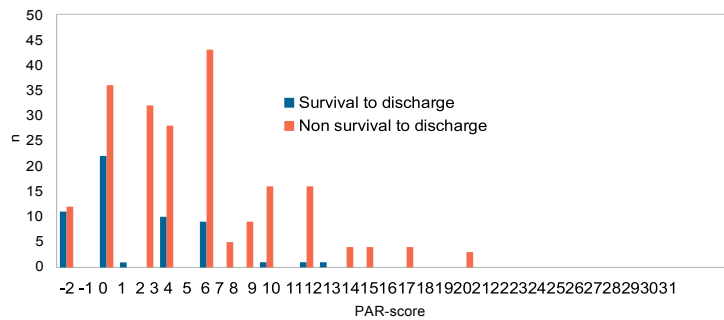**Fig. 1.** PAM-score and the distribution of survivors and non-survivors

Fig. 2. PAR-score and the distribution of survivors and non-survivors

While increasing heart rate (HR) was associated with increased risk of non-survival, increasing plasma concentration of sodium associated with better survival, suggesting that hyponatremia might be linked to poorer survival. We subdivided the patients with myocardial infarction (MI) into ST-elevation MI (STEMI) and non-ST elevation MI (NSTEMI) and as reported by Ebell[6] presence of STEMI, but not NSTEMI, was associated with increased survival after IHCA. Patients with independent Activities of Daily Life (ADL) had a better survival whereas patients with malignancies had markedly worse as compared to patients without.

4. Discussion

In accordance with previous studies, our results showed that PAM and PAR scores are not sufficient as the sole predictive instruments for estimation of survival and non-survival in IHCA[3,5,6] and

Table 2
PAM- and PAR-score compared to failure to survival to discharge.

	OR (CI 95%)	*p*	Sensitivity (%)	Specificity (%)
PAM-score > 1	2.03 (1.12–3.67)	**0.020a**	69.4	63.8
PAM-score > 2	2.67 (1.45–4.90)	**0.002a**	59.0	63.8
PAM-score > 3	2.10 (1.11–3.96)	**0.022a**	45.0	70.7
PAM-score > 4	3.54 (1.50–8.35)	**0.004a**	29.7	87.9
PAM-score > 5	6.03 (1.78–20.46)	**0.004a**	21.8	94.8
PAM-score > 6	6.49 (1.50–28.19)	**0.013a**	17.0	96.6
PAM-score > 7	3.85 (0.87–17.05)	**0.076a**	10.9	96.6
PAR-score > 2	2.87 (1.57–5.35)	**0.001b**	62.0	62.1
PAR-score > 3	3.88 (1.95–7.73)	**<0.001b**	49.8	79.3
PAR-score > 4	3.88 (1.95–7.73)	**<0.001b**	49.8	79.3
PAR-score > 5	8.53 (2.57–28.24)	**<0.001b**	31.0	94.8
PAR-score > 6	7.62 (2.30–25.27)	**0.001b**	28.8	94.8
PAR-score > 7	6.47 (1.94–21.59)	**0.002b**	24.9	94.8
PAR-score > 8	6.54 (1.53–28.02)	**0.011b**	17.9	96.6
PAR-score > 9	6.32 (1.47–27.08)	**0.013b**	17.5	96.6
PAR-score > 10	7.25 (0.96–54.99)	**0.055b**	10.5	98.3

a = Logistic regression, adjusted for sex and age b = logistic regression, adjusted for sex; OR = odds ratio.

Table 3
Basic characteristics.

Variable	Survival to discharge	Non-survival to discharge	*p*
No of patients	*n* = 58 (20.2)	*n* = 229 (79.8)	**NA**
Female sex (%)	*n* = 19 (32.8)	*n* = 92 (40.2)	**0.300b**
Mean Age (years)	65.4 (SD 15.0)	71.3 (SD 14.5)	**0.007a**
Initial cardiac rhythm (%)			
VF	*n* = 29 (50)	*n* = 26 (11.4)	**<0.001b**
VT	*n* = 10 (17.2)	*n* = 15 (6.6)	**0.010b**
PEA	*n* = 7 (12.1)	*n* = 68 (29.7)	**0.006b**
AS	*n* = 12 (20.7)	*n* = 120 (52.4)	**<0.001b**
Cardiac monitoring (%)	*n* = 42 (72.4)	*n* = 110 (48)	**0.001b**
All following on admission			
Heart rate (per bpm)*	78.9 (SD 26.6)	89.8 (SD 26.7)	**0.010a**
Pulse oxymetry (%)*	93.4 (SD 11.1)a	92.7 (SD 7.0)a	**0.031c**
P-Na (mmol l^{-1})*	138.5 (SD 4.6)	136.7 (SD 5.0)	**0.031a**
STEMI (%)	*n* = 14 (24.1)	*n* = 24 (10.5)	**0.006b**
Independent ADL (%)*	*n* = 54 (93.1)	*n* = 177 (77.3)	**0.007b**
Malignancy (%)*	*n* = 1 (1.7)	*n* = 44 (19.2)	**0.001b**

a = Independent T-test; VF = Ventricular fibrillation; b = Chi-square; VT = Ventricular tachycardia; c = Mann Whitney; PEA = Pulseless electrical activity; * = non-missing values > 80%; AS = Asystole; ADL = activities of daily life; STEMI = ST-elevation myocardial infarction.

their main caveat seems to be their low sensitivity. Still, the scores suggested could be useful as additive instruments. The PAR-score include fewer parameters and might therefore be easier to use clinically. With a PAR score >5, a more than 8-fold increase in the risk of non-survival to discharge was observed. The specificity of both scores increased with elevated scores, PAM- and PAR-scores >5 and above carried a specificity >90%, which can be helpful in order to identify patients with the highest risk of failure to survive IHCA.

Apart from evaluating the two scores, we tested individual components of the PAM- and PAR-scores and a number of new variables in relation to survival after IHCA. We validated some of the previous findings; such as increased survival in patients with STEMI,[6] with cardiac monitoring[9] and shockable rhythm,[1] and an increase in mortality in patients with malignancies and dependent ADL.[10] The explanation for higher survival in patients with STEMI, as compared with those without, is likely to be multifactorial. One of the reasons is probably the higher frequency of cardiac monitoring in patients with STEMI. Another reason is a higher frequency of VT or VF as initial cardiac rhythm in patients suffering from cardiac arrest in the presence of STEMI, and as expected we also found that presence of VF or VT ("shockable rhythm") was associated with higher survival rates.

Apart from presence of malignancies, we somewhat surprisingly found that many other severe comorbidities, such as chronic heart failure, chronic obstructive pulmonary disease, peripheral artery disease, chronic kidney disease, chronic cerebrovascular disease and diabetes mellitus, were not significantly related to reduced survival (Supplementary Table 2). This was also the case for some of the acute conditions such as acute renal failure, acute stroke, acute heart failure and sepsis with its subdivisions. Furthermore, a

number of the clinical variables which can indicate acute illness, such as C-reactive protein, *s*-potassium, *s*-creatinine, pulse oxymetry and blood pressure also did not show any significant relationship with likelihood of survival. In our study, as well as in clinical practice of emergency medicine, the cause of the acute illness and history taking of the patients chronic illnesses are sometimes uncertain and incomplete, which may explain why many severe comorbidities and acute illnesses turned out not to significantly aid in prediction of survival after IHCA. Another contributing reason could be that the samples size in the current study did not provide statistical power enough to identify more modest effect sizes of such conditions and variables in relation to the outcome. Other limitations, which hamper generalizability of our results to all patients with IHCA following CPR, are missing values, especially concerning the laboratory variables but also some clinical variables as the practical difficulties involved in measuring such parameters are greatest in the most critically ill patients. In addition, the material in this study is somewhat selected from the beginning since Do-Not-Resuscitate (DNR)-orders are decided early on in the most ill and elderly patients and therefore these patients were not included in this study.

Interestingly, we found a significant association between low plasma sodium concentration and increased risk of non-survival to discharge after IHCA, a finding which has never been reported before. The cause of the relationship remains unclear and needs replication in other studies but hyponatremia has previously been linked to elevated risk of mortality after hospitalization[11] and to mortality in patients with heart failure.[12]

The finding of a significant association between lower HR and increased survival is intriguing. Decreased mortality with

Table 4
Significant variables in relation to failure to survive to discharge in uni- and multivariate logistic regression analysis.

Variable	Crude		Adjusted for sex and age	
	OR (95% CI)	**p**	**OR (95% CI)**	**p**
Age (years)	1.025 (1.006–1.044)	**0.009**	1.025 (1.006–1.044)	**0.010**
Non shockable vs shockable cardiac rhythm	9.41 (4.94–17.92)	**<0.001**	9.86 (5.08–19.12)	**<0.001**
Cardiac monitoring	0.35 (0.19–0.66)	**0.001**	0.38 (0.20–0.72)	**0.003**
Heart rate (per bpm)	1.019 (1.004–1.034)	**0.010**	1.024 (1.009–1.040)	**0.002**
Pulse oxymetry (%)	0.99 (0.94–1.03)	0.599		
P-Na (mmol l^{-1})	0.92 (0.86–0.99)	**0.032**	0.92 (0.85–0.99)	**0.023**
STEMI	0.37 (0.18–0.77)	**0.008**	0.32 (0.15–0.69)	**0.004**
Independent ADL	0.25 (0.09–0.73)	**0.011**	0.27 (0.09–0.78)	**0.016**
Malignancy	13.56 (1.83–100.60)	**0.011**	13.86 (1.86–103.46)	**0.010**

beta-blocking agents in patients with heart failure[13,14] and ischemic heart disease[15] is a known fact—and could be speculated to contribute to this association.

5. Conclusions

Neither the PAM- nor the PAR-score seems to sufficiently discriminate between in-hospital death and survival after IHCA and thus cannot be used alone as clinical tools guiding CPR decisions in patients with IHCA. We confirm that malignancy was associated with increased in-hospital mortality, and cardiac monitoring, shockable rhythm, presence of STEMI and independent ADL, with decreased in-hospital mortality. These findings may aid us in our understanding of which patients who will benefit the most from CPR, and who will not. Finally, our results also suggest that HR and plasma sodium concentration upon admission may represent new tools for risk stratification.

Conflict of interest statement

No conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.resuscitation.2014.07.009.

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Paper II

Validation of the good outcome following attempted resuscitation score on in-hospital cardiac arrest in southern Sweden

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article info

abstract

Background: There is a great need for a simple and clinically useful instrument to help physicians estimate the probability of survival to discharge with a good neurological outcome (cerebral performance category, CPC = 1) in cases of in-hospital cardiac arrest (IHCA). Our aim was to validate the "Good Outcome Following Attempted Resuscitation" (GO-FAR) score in a different country with different demographics than previously investigated.
Methods: A retrospective observational study including all cases of IHCA who were part of a cardiac arrest registry at Skåne University Hospital in Sweden 2007–2010.
Results: Two-hundred-eighty-seven patients suffered IHCA during the period. A majority were male and mean age was 70 years. Overall survival to discharge independent of neurological function was 20.2%; 78% of the survivors had CPC = 1 and survival to discharge with CPC = 1 was 15.7%. The area under the receiver operating characteristics curve for the GO-FAR score was 0.85 (CI = 0.78–0.91, p b 0.001), consistent with very good discrimination. Patients in the group with low or very low probability of survival had a likelihood of 2.8% (95% CI 0.0–6.7), whereas the groups with average and above average probabilities had likelihoods of 8.2% (3.7-13) and 46% (34–58), respectively, for good neurological outcome. This compares with likelihoods of 1.6%, 9.2% and 27.8% in the original study.
Conclusion: The GO-FAR score accurately predicted the probability of survival to discharge with CPC = 1, even when applied to a different population in another country.

1. Introduction

For many years, there has been a need for a systematic approach to the problem of risk stratification for hospitalized patients who experience a sudden cardiac arrest – who is most likely to benefit from cardiopulmonary resuscitation (CPR) and who is not, and in particular, who is likely to survive an in-hospital cardiac arrest (IHCA) with intact neurological and cognitive functions. Today, decisions to initiate CPR or to abstain from it by writing a do-not attempt resuscitation (DNAR) order are sometimes arbitrary, since there are no clinical scoring systems or official recommendations to rely on. In everyday clinical practice, decisions are made based on the patient's age and comorbidities. While this may seem to be clinically reasonable, it lacks scientific support and inevitably leads to different decisions in similar clinical scenarios. In addition, previous studies [1-3] have shown that physician and patient estimates of the likelihood of survival are inaccurate and inconsistent.

Several scoring systems have been suggested to identify patients at the highest risk of not surviving in-hospital CPR. In 1989, George and colleagues [4] suggested the Pre-arrest Morbidity-score (PAM) consisting of 15 different variables. The variables included were previously shown to be associated with survival in a previous study of CPR outcomes [5], with the remainder added based on the authors' expert opinion. In 1992, the Prognosis after Resuscitation (PAR) score was suggested by Ebell [6]. This time, a more systematic approach was used to identify clinical predictor variables; the score was elaborated from 14 studies of CPR outcome included in a meta-analysis.

Unfortunately, none of these scoring systems provided the accuracy needed for usage in everyday clinical practice as shown by a subsequent validation study [7]. They found low overall accuracy, with a decreasing sensitivity and increasing specificity as the score increased. These scoring systems also did not take into consideration the patient's neurological and cognitive function after a successful resuscitation.

Recently, a newly devised scoring system named the "Good Outcome Following Attempted Resuscitation" (GO-FAR) score was developed [8].

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[1] This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

This study used the "Get With the Guidelines-Resuscitation registry", a national cardiac arrest registry in USA comprising 366 hospitals and including 51,240 patients suffering an IHCA between 2007 and 2009. This score had an area under the receiver operating characteristics curve (AUROC) of 0.78 and consisted of only 13 variables with a score ranging from −15 to 40. In the split sample internal validation, it accurately predicted the probability of a successful resuscitation with a good cerebral outcome.

At Skåne University hospital in Malmö, Sweden, there are approximately 70-80 cases of IHCA per year. In 2013, we evaluated the PAM and PAR scores and other clinical variables on all the cases of IHCA occurring between 2007 and 2010 [9]. In our analysis of 287 cases we found that these scores lacked predictive accuracy, as shown in previous validation studies [7,10]. We now have evaluated the GO-FAR score on the same material.

2. Methods

This is a retrospective observational study including all patients 18 years and older experiencing IHCA and treated with CPR between 2007 and 2010 at Skåne University Hospital, Malmö, Sweden. The local ethics committee of Lund University approved the study. The procedure of selection and inclusion was thoroughly described in our previous work [9]. In short, cases of IHCA were identified and analyzed through access to the local cardiac arrest registry and medical record software "Melior". In the local cardiac arrest registry, 825 cases were recorded. These cases were then reviewed by a doctor and of the 825 cases 538 were excluded due to the following reasons: 477 were out-of-hospital cardiac arrests, 8 were duplicates, 9 were patients b18 years of age, 30 were not real cardiac arrests, 6 were canceled CPR, 6 were suicides and 2 cases were excluded because no information was available in the data base. A total number of 287 cases remained for further analysis. The cerebral outcome was measured using the "cerebral performance category" (CPC) scale shown in Table 1.

The GO-FAR score was calculated for each case according to Table 2. The definitions were the same as used by Ebell and colleagues in the original development and internal validation study [8], but with some minor changes. For "Septicemia" we used the international definitions according to Levy [11]. For the variables "Hypotension and hypoperfusion", "Renal insufficiency", "Hepatic insufficiency" and "Respiratory insufficiency" we collected data within the most recent 48 h prior to arrest in order to avoid missing data.

For symmetrically distributed continuous variables, mean and standard deviation (SD) were used as descriptive measures, whereas median and interquartile range (IQR) were used for skewed distributions. The area under the receiver operating characteristics (ROC)-curve (C statistic) was calculated for the continuous GO-FAR score. The GO-FAR score compared to survival to discharge with CPC = 1 was also analyzed using logistic regression analysis. A two-sided p-value b 0.05 was considered as nominally statistically significant. The score was then subdivided into groups previously described [8] and frequencies for the different categories listed. All analyses were performed using SPSS statistical software version 21.0 for Windows (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.).

3. Results

Demographic characteristics of our population as well as of those in the original population used to develop the GO-FAR score are shown in Table 3. Most patients were male and the mean age was 70.1 years (SD 14.8). The overall survival rate to discharge independent of CPC was 20.2%, and survival to discharge with CPC = 1 (good neurologic outcome) was 15.7%. Among the survivors with CPC = 1, 66.6% had an initial cardiac rhythm of either ventricular fibrillation or ventricular tachycardia. Among the non-survivors 79.3% had a non-shockable cardiac rhythm of asystole or pulseless electrical activity. The median value of the GO-FAR score

Table 1
Cerebral performance category (CPC) scale.

CPC 1	Good cerebral performance: conscious, alert, able to work, might have mild neurologic or psychologic deficit
CPC 2	Moderate cerebral disability: conscious, sufficient cerebral function for independent activities of daily life. Able to work in sheltered environment
CPC 3	Severe cerebral disability: conscious, dependent on others for daily support because of impaired brain function. Ranges from ambulatory state to severe dementia or paralysis.
CPC 4	Coma or vegetative state
CPC 5	Brain death

Table 2
GO-FAR score.

Variable	Score
Neurologically intact at admission (CPC = 1)	−15
Major trauma	10
Acute stroke	8
Metastatic or hematologic cancer	7
Septicemia	7
Medical noncardiac diagnosis	7
Hepatic insufficiency	6
Admitted from skilled nursing facility	6
Hypotension or hypoperfusion	5
Renal insufficiency or dialysis	4
Respiratory insufficiency	4
Pneumonia	1
Age, years	
70-74	2
75-79	5
80-84	6
≥85	11

was 3 with an interquartile range of 18. The GO-FAR score compared to survival with CPC = 1 and adjusted for sex yielded an odds ratio of 0.86 per additional point (95% confidence interval (CI) 0.82-0.90, p b 0.001).

The distribution of the GO-FAR score among the cases is shown in Fig. 1. Table 4 describes the frequencies and their relation to different risk groups. Approximately 25% of patients were classified as low or very low probability of survival neurologically intact, and in this group only 2 of 71 patients had a good outcome (2.8%) (95% CI 0.0-6.7). This compares with a likelihood of 1.6% in the original study [8].

The ROC-curve of the continuous GO-FAR score is shown in Fig. 2, with an area under the curve 0.846 (CI = 0.78-0.91). The sensitivities and specificities for various cutpoints of the GO-FAR score were calculated and are shown in Supplementary Table 1. As expected, the specificity increased and the sensitivity decreased as the score increased. The best accuracy was achieved at a score of − 3.5, where sensitivity was 79% and specificity was 78%.

4. Discussion

This study shows that the GO-FAR score is a reliable and accurate method for identifying those patients with "very low", "low", "average" and "above average" probabilities of survival of IHCA with good neurological function measured as CPC = 1. The score has now been validated on a smaller sample than in the original article [8], but in a different country and with different demographics.

There are important differences between the US data from the original study [8] and the Swedish data in this study, as seen in Table 3. The Swedish population was somewhat older, more likely to be male, and had a significantly higher rate of survival to discharge with CPC = 1 than the US population. The latter in particular may affect calibration of the GO-FAR score in this population. The US population also had a large

Table 3
Demographic characteristics.

Characteristic	Swedish cohort (n = 287)	Original US cohort (n = 51,240)
Male sex (%)	61.3	58.3
Mean age (years)	70.1	65.0
Race (%)		
White/Caucasian	N/A[a]	72.8
Black/African-American		23.3
Other		3.9
Overall survival (%)	20.2	18.5
Survival with CPC = 1 (%)	15.7	10.4

[a] Not available in the dataset, but presumably largely White/Caucasian given the demographic make-up of Sweden.
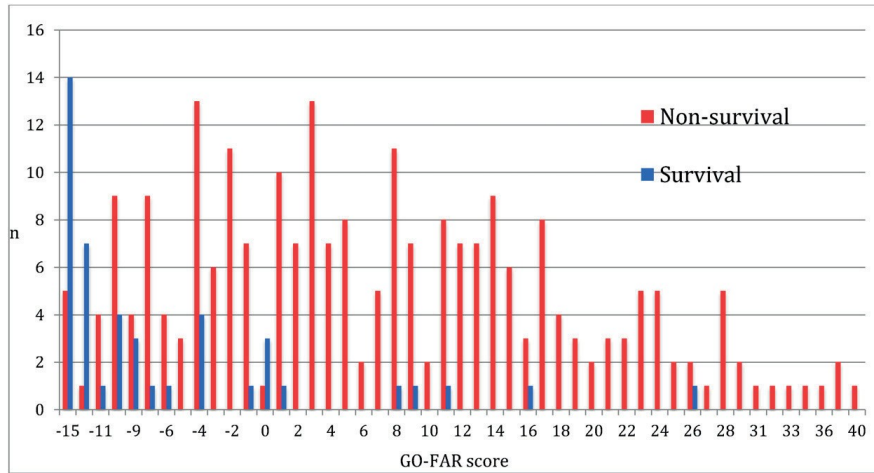
Fig. 1. Distribution of GO-FAR scores compared to survival.

population of African-Americans, a group that has a lower likelihood of survival to discharge [8,12].

Our results in this study are partly stronger with a higher ROC (corresponding to the c-statistic) than in the original dataset [8], which may be due to a more precise data collection. Since the number of patients is much smaller, a medical doctor has been able to review every case.

5. Study limitations

The sample size itself could be regarded as a limitation. The survival rate in the group of "very low" probability of survival was surprisingly higher (3.8%) than in the group of "low" probability of survival (2.1%). In both groups there was only a single survivor (both under the age of 40 years), and if the "very low" and "low" probability groups were combined the survival with CPC = 1 would be 2.8% (95% CI 0.0-6.7). This confidence interval includes the confidence interval for this group from the original interval validation of 1.6% (95% CI 1.4-1.8). We reanalyzed the original validation data from the GWTG registry, stratifying by age ᵇ 40 years vs ≥ 40 years. For younger patients, the c-statistic was 0.75, while for patients 40 years or older it was somewhat higher at 0.78. For patients under age 40 years classified as low or very low probability of good neurologic outcome, the actual likelihood was 2.5% compared with 1.3% for those 40 years and older. Thus, it seems prudent to use caution when applying the GO-FAR score to patients under age 40 years [8].

Another limitation has been the classification of patients into CPC groups. CPC is not routinely measured upon admission and is seldom noted in the medical records when a patient surviving IHCA is discharged. Nonetheless, there is a strict routine to note the status of "activities of daily life" (ADL), which can help to classify the patients correctly (CPC 2 and CPC 3). There are sometimes still difficulties to correctly assess the CPC score when the patient is admitted.

A "good neurological outcome" has traditionally been defined as CPC = 1–2 [13]. A recent study [14] has shown that there are still

Table 4
Rates of survival to discharge with CPC = 1 by GO-FAR risk group.

GO-FAR score (points)	Risk group	Patients in risk group (%)	Survivors/total in risk group	Survivors (%) (95% CI)
≥ 24	Very low	9.1	1/26	3.8 (0.0-11)
14 to 23	Low	16.4	1/47	2.1 (0.0-6.3)
≥ 14	Very low or low	25.5	2/73	2.8 (0.0-6.7)
−5 to 13	Average	51.2	12/147	8.2 (3.7-13)
−15 to −6	Above average	23.3	31/67	46 (34-58)

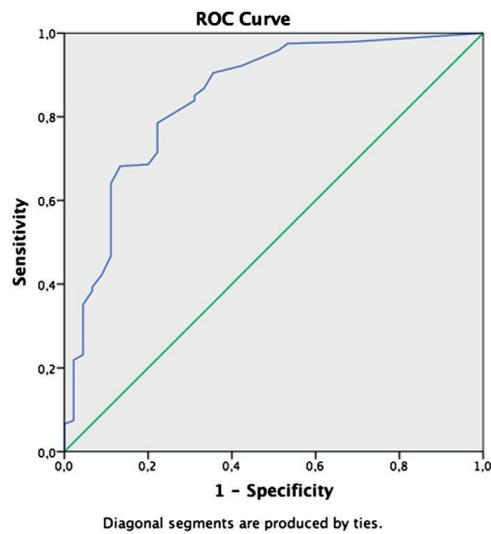* Probability of survival to discharge with CPC = 1.

Fig. 2. Receiver operating characteristic curve for the GO-FAR score.

considerable cognitive deficits in the group with CPC of 2 at discharge, while the group of CPC of 1 seem to perform as well as the control group. This finding supports the use of the GO-FAR score since it is designed to only identify those with survival and CPC of 1 at discharge. Finally, a prospective design would better minimize a number of biases.

However, as in the original study [8], this was practically impossible to achieve.

6. Conclusions

The idea of using a scoring system to assist patients and clinicians in the decision making regarding resuscitation and do-not-resuscitate (DNR) orders is logical but complicated. There is a great need of expanding the knowledge about how present comorbidities and age influence the outcome and the probability of survival with no significant cognitive deficits defined as CPC of 1. It is also important to study whether this approach is acceptable to patients and physicians. No scoring system is able to predict the outcome of a specific individual with perfect accuracy; survival as well as cognitive status depends on a variety of peri- and post-arrest variables not knowable prior to arrest. But we are now able to accurately enough predict the probability of survival with a good neurological outcome, which serves as a good scientific basis for the discussion with the individual patient.

The GO-FAR score is to our knowledge the best instrument available for prediction of probability of survival of IHCA with a good neurological outcome. We would recommend this to be used upon admission of patients to hospital in order to have a scientific decision basis for the discussion of do-not-resuscitate orders. It should be used with caution in patients under the age of 40 years.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ijcard.2016.06.146.

Conflicts of interest

The authors report no relationships that could be construed as a conflict of interest.

Acknowledgement

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Paper III
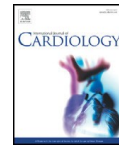
Midlife risk factor exposure and incidence of cardiac arrest depending on cardiac or non-cardiac origin

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abstract

Objective: Little is known about midlife risk factors of future cardiac arrest. Our objective was to evaluate cardiovascular risk factors in midlife in relation to the risk of cardiac arrest (CA) of cardiac and non-cardiac origin later in life.

Methods: We cross-matched individuals of the population based Malmö Diet and Cancer study (n = 30,447) with the local CA registry of the city of Malmö. Baseline exposures were related to incident CA.

Results: During a mean follow-up of 17.6 ± 4.6 years, 378 CA occurred, of whom 17.2% survived to discharge. Independent midlife risk factors for CA of cardiac origin included coronary artery disease {HR 2.84 (1.86-4.34) (p b 0.001)}, diabetes mellitus {HR 2.37 (1.61-3.51) (p b 0.001)} and smoking {HR 1.95 (1.49-2.55) (p b 0.001)}. Dyslipidemia and history of stroke were also significantly associated with an elevated risk for CA of cardiac origin.

Independent midlife risk factors for CA of non-cardiac origin included obesity (BMI N 30 kg/m^2) {HR 2.37 (1.51-3.71) (p b 0.001)}, smoking {HR 2.05 (1.33-3.15) (p b 0.001)} and being on antihypertensive treatment {HR 2.25 (1.46-3.46) (p b 0.001)}.

Conclusion: Apart from smoking, which increases the risk of CA in general, the midlife risk factor pattern differs between CA of cardiac and non-cardiac origin. Whereas CA of cardiac origin is predicted by history of cardiovascular disease, dyslipidemia and diabetes mellitus, the main risk factors for CA of non-cardiac origin are obesity and hypertension. In addition to control of classical cardiovascular risk factors for prevention of CA, our results suggest that prevention of midlife obesity may reduce the risk of CA of non-cardiac origin.

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1. Introduction

Sudden cardiac arrest, defined as "the cessation of cardiac mechanical activity as confirmed by the absence of signs of circulation" [1], is a rare but potentially reversible condition if treated with cardiopulmonary resuscitation (CPR). The progression of the condition could lead to sudden cardiac death (SCD) [2], which in turn is defined as a sudden arrest of presumed cardiac origin occurring within 24 h after onset of any symptoms that could retrospectively be interpreted as being of cardiac origin [3]. Cardiac arrest is commonly subdivided into in-hospital cardiac arrest (IHCA) and out-of-hospital cardiac arrest (OHCA). The incidence of IHCA is about 1–5/1000 admissions [4] and for OHCA 0,5/1000 population [5]. Depending on location, the survival rates ranges

from 10,3% (OHCA) to 28% (IHCA) according to the 2013 report from the Swedish Cardiac Arrest Registry (SCAR) [4]. Other sources claim lower survival rates such as 5–10% for OHCA [4] and 15–20% for IHCA [5].

The main cause of cardiac arrest is believed to be cardiac disease, which accounts for approximately 2/3 of all cases [4]. Cardiac arrest with a non-cardiac etiology constitutes about 15–25% of cases and the etiology includes bleedings, intracranial hemorrhages and pulmonary embolism [6].

Many researchers have investigated cardiac arrest, both IHCA and OHCA, however, mainly focusing on overall survival and peri-arrest factors such as early defibrillation [7-9]. One limitation is that comorbidities, cardiovascular risk factors and current medications rarely are known. Another limitation is that these studies are usually burdened with a selection bias since the patients included already have experienced OHCA or IHCA and therefore represent a more morbid selection. So far, no study has prospectively examined cardiovascular risk factor pattern in relation to incidence of CA during long-term follow-up. Here, we addressed this issue by relating cardiovascular risk factor

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exposure in midlife to risk of CA of cardiac and non-cardiac origin later in life in a large population-based prospective cohort study. In addition, midlife cardiovascular risk factors as well as peri-arrest factors were related to survival in subjects who did suffer a CA.

2. Materials and methods

2.1. Inclusion

The Malmö Diet and Cancer study (MDCS) is a community-based, prospective observational study of 30,447 participants drawn from ~ 230,000 residents of Malmö, Sweden. Men aged 46 to 73 years and women aged 45 to 73 years were invited to participate and were enrolled between 1991 and 1996. Details of the MDC design have been previously reported [10]. The baseline investigation included a physical exam, anthropometry, blood pressure measurement, blood sampling including measurement of apolipoproteins and a questionnaire in which the participants answered questions about their lifestyle, diet, socioeconomic factors, current medication, current health and previous diseases.

The local cardiac arrest registry at Skåne University Hospital, Malmö, was created in 1999 and covers 2758 cases of cardiac arrest up until 2012. All suspected cardiac arrests result in initiation of an automatic alarm, which reaches the emergency team. After completing the resuscitation, data from every case is registered and sent to the local cardiac arrest registry. A specialized nurse reviews the data, further data is then collected from the medical records and a report is sent to the national cardiac arrest registry including information about outcome, initial cardiac rhythm, time to defibrillation and place of the arrest noted.

Using the Swedish personal identification number, we cross-matched individuals of the MDCS material with the local cardiac arrest registry of the city of Malmö. The local ethics committee of Lund University approved the study. The participants provided written consent upon inclusion in the MDCS but no consent was obtained for our study since most of the participants were deceased. This procedure was approved by the ethics committee.

In the MDCS there were 518 incident cases of cardiac arrest. A medical doctor then reviewed each case in the medical records system "Melior". The following cases were excluded: 75 cases were not real cardiac arrests (seizures, fainting, stroke, non-pulseless VT, bradycardia), 34 cases were duplicates, 13 cases were lacking data. 11 cases had 2 separate cardiac arrests, of which only the first was included, 3 cases were suicides, 1 case was a procedure related accident (PCI) and 3 cases were accidents. Thus, 378 cases remained for further analysis. Cause of death was recorded by reviewing the autopsy reports of each individual case. In cases where no autopsy had been performed the cause of death was only recorded if clinically determined as "Sudden cardiac death" according to the previously mentioned definition [2]. In cases where the cause of death was not clinically determined nor autopsy was performed, we used the Utstein definition of cardiac origin [1]. All the cases of cardiac arrest were then divided into arrest of cardiac or non-cardiac origin.

Relevant baseline exposure data were obtained from the MDCS baseline exam where- as, factors with close temporal relationship to the cardiac arrest, i.e. periarrest factors, were collected from the local cardiac arrest registry and additional data related to the cardiac arrest were collected from the medical records. Variables with missing values exceeding 20% were excluded from analysis.

2.2. Definitions

Obesity was defined as a body mass index (BMI) higher than 30 (kg/m^2). Diabetes mellitus was defined as self-report of a physician's diagnosis of diabetes, having a fasting whole blood glucose of ≥ 6.1 mM (corresponding to plasma glucose of ≥ 7.0 mM) or being on antidiabetic medication. Hypertension was defined as being on antihypertensive medication. Socioeconomic variables (living alone, education) and current use of medications were retrieved from the MDCS baseline questionnaire. Blood samples were collected from MDCS participants at baseline and serum and plasma was separated within 1 h and stored at −80 °C. Serum concentrations of apolipoprotein A1 (ApoA1) and B (ApoB) were measured by Quest Diagnostics (San Juan Capistrano, CA), blinded to case-control status, using an immunonephelometric assay run on the Siemens BNII (Siemens, Newark, DE). The inter-assay variability was b4.0% for both ApoA1 and ApoB.

Occurrence of cardiovascular diseases prior to the MDCS baseline exam was assessed by linking the Swedish personal identification number with the national inpatient registry. CAD was defined as fatal or non-fatal myocardial infarction or having had coronary artery by-pass grafting (CABG) or percutaneous coronary intervention (PCI). Myocardial infarction was defined on the basis of International Classification of Diseases 9th and 10th Revisions (ICD9 and ICD10) codes 410 and I21, respectively. PCI was defined based on the operation codes FNG05 and FNG02. CABG was identified from national Swedish classification systems of surgical procedures, the KKÅ system from 1963 until 1989 and the Op6 system since then. CABG was defined as a procedure code of 3065, 3066, 3068, 3080, 3092, 3105, 3127, 3158 (Op6) or FN (KKÅ97). Congestive heart failure was defined as diagnosis codes 427.00, 427.10 and 428.99 for International Classification of Diseases 8th Revision (ICD-8), 428 for the ICD9 and I50 and I11.0 for the ICD-10. Stroke was assessed using codes 430, 431, 434 and 436 (ICD9) and I60, I61, I63, and I64 (ICD10). Atrial fibrillation and atrial flutter was defined using diagnosis codes 427.92 (ICD-8), 427D (ICD-9) and I48 (ICD-10).

2.3. Statistical analysis

Mean and standard deviation (SD) were used as descriptive measures for normally distributed continuous variables, whereas median and interquartile range (IQR) was used for skewed distributions. For continuous variables Students t-test or Mann-Whitney test was used to compare group means (medians) and Chi-square test and Fischer's exact test were used for comparison of group frequencies. Variables, which displayed significant differences between groups, were then analysed using either Cox proportional hazards model or logistic regression analysis creating a model of independent risk factors. Cox regression was used for event analyses with long term follow-up, while logistic regression was judged more appropriate in analyses that were not time dependent. A two-sided p-value b0.05 was considered as nominally statistically significant. All analyses were performed using SPSS statistical software version 21.0 for Windows (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.).

3. Results

In the MDCS material, 60.2% were female and mean age at the time of screening was 58.0 years (SD 7.6). The mean follow-up time was 17.6 years (SD 4.6). The midlife characteristics, i.e. baseline characteristics (1991-1996) are shown in Table 1, with the population divided into subjects who did not develop cardiac arrest during follow up and those who developed cardiac arrest of cardiac and non-cardiac origin.

During follow-up, over-all 378 incident cases of cardiac arrest occurred, and of these 65.9% were males. Mean age at cardiac arrest was 74.6 years (SD ± 7.1) and 63.5% were OHCA. Return of spontaneous circulation (ROSC) was reached in 37.3% of CA cases, but in total, only 17.2% were discharged alive from the hospital. The cause of the arrest was determined to be cardiac in 68.7% of the cases. Independently of IHCA or OHCA, an initial shockable rhythm of either ventricular fibrillation (VF) or ventricular tachycardia (VT) occurred in 26.2%, while 59.5% had asystole and 14.3% pulseless electrical activity (PEA). Nineteen percent of the cases were admitted to a ward with supervision by telemetry. Survival to discharge differed depending on the origin of CA; 21% survived among the patients suffering a CA of cardiac origin while only 7.5% survived among those with CA of non-cardiac origin. Concerning presenting diagnosis, 20.1% of the patients had ST-elevation myocardial infarction (STEMI), followed by non ST-elevation myocardial infarction (NSTEMI) (9.3%), chronic heart failure (7.4%) and chronic ischemic heart disease (6.6%). The non-cardiac causes were dominated by respiratory failure (6.3%), pulmonary embolism (5.3%) and ruptured aortic aneurysm (4.5%). The causes of death are listed in Table 2.

Next, the baseline characteristics from Table 1 were related to likelihood of survival to discharge among subjects who suffered a cardiac arrest. The only baseline factor that showed a significant association with outcome in a univariate model was low level of ApoA1 (mg/L); a lower value seemed to be associated with better survival ($p = 0.037$) (Supplementary Table 1). Adding ApoA1 (mg/L) to a Cox regression analysis against survival to discharge and adjusting for sex and age, produced a model with HR 0.983 (95% CI 0.972-0.995, $p = 0.006$) (Supplementary Table 2).

In Table 3 the final multivariate models for risk of arrest of cardiac and non-cardiac origin are presented. The risk profiles differ greatly; arrest of cardiac origin seem to be clearly associated with prevalent cardiovascular disease and classical risk factors for developing cardiovascular disease such as male sex, age, dyslipidemia, diabetes and smoking. In the risk profile of arrest of non-cardiac origin, the most important factors seem to be smoking, obesity and being on antihypertensive treatment. Exclusion of cases of CA of non-cardiac and cardiac origin respectively from the "non-event comparison group" did not change the results (data not shown).

In Table 4, the relationship between all known pre- and peri-arrest factors known and survival are listed. Adding those variables from Table 4 showing a significant association with survival and adjusting for sex and age at cardiac arrest produced a model shown in Table 5. Shockable rhythm, arrest of cardiac origin and history of atrial fibrillation or flutter improved survival to discharge whereas OHCA reduced it.

Table 1
Basic characteristics, univariate analysis.

Variable	Control group	Arrest of cardiac origin		Arrest of non-cardiac origin	
	(n = 30,069), n (%)	(n = 272), n (%)	p	(n = 106), n (%)	p
Male sex	n = 11,872 (39.5)	n = 194 (71.3)	b0.001*	n = 55 (51.9)	0.011*
Age (years)||	57.6 (12.9)	62.3 (9.4)	b0.001†	62.6 (9.6)	b0.001†
Finished elementary school or higher (yes/no)	27,905 (99,1)	254 (98.8)	0.582*	97 (100)	0.360*
Living alone (yes/no)	6965 (24,7)	43 (16.7)	0.003*	17 (17.5)	0.105*
Smoking (yes/no)	7961 (28,2)	93 (36.0)	0.006*	33 (34.0)	0.211*
Obesity (yes/no)	4167 (13,9)	47 (17.3)	0.110*	31 (29.2)	b0.001*
ApoA1 (mg/L)	156.8 (SD 28.2)	146.1 (SD 26.5)	b0.001‡	152.5 (SD 25.2)	0.149‡
ApoB (mg/L)	107.1 (SD 26.1)	117.6 (SD 25.1)	b0.001‡	108.2 (SD 21.6)	0.701‡
Systolic BP (mm/Hg)	141.0 (SD 20.0)	150.2 (SD 21.0)	b0.001‡	149.1 (SD 21.6)	0.145‡
Antihypertensive treatment (yes/no)	4558 (15,2)	68 (25.0)	b0.001*	35 (33.0)	b0.001*
Lipid lowering treatment (yes/no)	891 (3,0)	23 (8.5)	b0.001*	5 (4.7)	0.306*
Antidiabetic treatment (yes/no)	476 (1,6)	19 (7.0)	b0.001*	6 (5.7)	0.001*
Antiplatelet drug therapy (yes/no)	721 (2,6)	16 (6.3)	b0.001*	4 (4.0)	0.331*
History of prevalent CAD (yes/no)	732 (2,4)	33 (12,1)	b0.001*	8 (7,5)	0,001*
History of prevalent stroke (yes/no)	315 (1.0)	12 (4,4)	b0.001*	6 (5,7)	b0.001*
History of prevalent heart failure (yes/no)	83 (0.3)	3 (1.1)	0.043§	1 (0.9)	0.262§
History of prevalent atrial fibrillation or flutter (yes/no)	306 (1,0)	5 (1.8)	0.181*	1 (0.9)	1.00§
History of prevalent diabetes mellitus (yes/no)	1293 (4,3)	37 (13.6)	b0.001*	10 (9.4)	0.011*

* = Chi square, † = Mann-Whitney, ‡ = Students t-test, § = Fischer's exact test, || = median (interquartile range).
BP = blood pressure, CAD = coronary artery disease.

4. Discussion

To our knowledge, this is the first study examining mid-life risk factors for cardiac arrest during long-term follow-up, as well as examining separately risk factors for cardiac arrests of cardiac and non-cardiac origin, respectively. We find a clear difference in midlife risk factors between cardiac arrest of cardiac and non-cardiac origin. In the group with arrest of cardiac origin the results show a typical cardiovascular risk factor pattern. In addition, a finding that surprised us was that living alone seems to be associated with a lower risk of CA of cardiac origin. The reason for this finding remains unclear, but in a subanalysis women were living alone in more often than men (28.3%, vs 18.9% p b 0.001) and thus female sex, which by itself is protective against CA, may be one explanation. We therefore tested for interaction between the variable of living alone and both gender and age on the outcome of CA of cardiac origin and found a non-significant interaction with gender (p = 0.150) and a significant interaction with age (p = 0.008). Subsequent stratification of the age variable (above or below mean age) in a Cox regression analysis showed that patients older than the mean age of 58 years explained the interaction of age on the "living alone"-variable

Table 2
Causes of death.

	n (%)
Arrest of cardiac origin (n = 215)	
Sudden cardiac death	96 (44.6)
ST-elevation myocardial infarction	56 (26)
Chronic ischemic heart disease	24 (11.2)
Non-ST-elevation myocardial infarction	22 (10.2)
Chronic heart failure	13 (6.0)
Acute heart failure	2 (0.9)
Arrhythmia	2 (0.9)
Arrest of non-cardiac origin (n = 98)	
Respiratory failure	22 (22.4)
Pulmonary embolism	21 (21.4)
Ruptured aortic aneurysm	17 (17.3)
Malignancy	7 (7.1)
Unknown	7 (7.1)
Pneumonia	6 (6.1)
Gastrointestinal hemorrhage	5 (5.1)
Hemorrhagic shock of unknown origin	5 (5.1)
Cerebral hemorrhage	3 (3.1)
Septicemia	3 (3.1)
Aortic dissection	2 (2.0)

(age b 58 years: HR 1.29 CI 0.76-2.19, p = 0.34, age N 58 years: HR 0.45, CI 0.28-0.72, p = 0.001).

In the group with cardiac arrest of non-cardiac origin, midlife smoking exposure and antihypertensive treatment are important risk factors. Interestingly, obesity was also significantly associated with an elevated risk of arrest of non-cardiac origin. Although our study is observational, and thus cannot prove causality between exposures and outcome, they suggest an important clinical implication; i.e. that apart from intensive cardiovascular risk factor control for prevention of cardiac arrest of cardiac origin, reduction of midlife obesity might prevent the risk of cardiac arrest of non-cardiac origin.

The cardiovascular risk factor pattern for arrest of cardiac origin resembles that in previous studies of sudden cardiac death. Although sudden cardiac death is a different entity (e.g. by definition always being fatal) than arrest of cardiac origin, these similarities in midlife risk factor pattern might be expected as there is overlap between the two [11-13]. This finding emphasizes the importance of aggressive preventive measures of cardiovascular risk factors since the ultimate outcome in the shape of a cardiac arrest carries such a high mortality rate.

Identification of midlife risk factors for cardiac arrest of non-cardiac origin is on the other hand completely new. Obesity is a growing global problem [14] and our finding adds cardiac arrest of non-cardiac origin as a novel and severe risk associated with being obese which further underlines the need of population strategies and individual patient efforts to prevent and treat obesity. Furthermore, our data encourages inclusion of cardiac arrest of non-cardiac origin, as well as its potential underlying triggering diseases, in ongoing and planned surgical and pharmacological intervention trials for weight reduction.

It could be speculated that obesity is related to the most common cause of arrest of non-cardiac origin in our material, which was respiratory failure [15]. Pulmonary embolism was the second most common cause and its relation to obesity and hypertension has previously been investigated by several authors, among them Ageno et al. [16]. Finally, smoking and hypertension are known risk factors for aortic aneurysm development [17], which could explain why ruptured aortic aneurysm was the third most common cause of arrest of non-cardiac origin.

Concerning factors at arrest, shockable rhythm and cardiac origin were clearly favorable for survival while out-of-hospital cardiac arrest was not. The increased survival of an arrest of cardiac origin could then possibly explain the finding of a lower ApoA1 being associated with improved survival. Interestingly, a history of atrial fibrillation or flutter was significantly associated with increased survival. The cause for this observation remains unclear, but there are probably confounders. Several

Table 3
Final multivariate predictors for arrests of cardiac and non-cardiac origin.

Variable	Cardiac origin		
	HR	CI (95%)	p
Male sex	2.59	1.93-3.48	♭0.001
Age (years)	1.09	1.07-1.11	♭0.001
Living alone (yes/no)	0.68	0.48-0.96	0.026
Smoking (yes/no)	1.95	1.49-2.55	♭0.001
ApoA1 (mg dL)	0.99	0.99-1.00	0.009
ApoB (mg dL)	1.01	1.01-1.02	♭0.001
Antihypertensive treatment (yes/no)	1.19	0.88-1.61	0.257
History of stroke (yes/no)	1.60	1.32-1.94	♭0.001
History of CAD (yes/no)	2.84	1.86-4.34	♭0.001
History of heart failure (yes/no)	2.84	1.86-4.34	0.178
History of diabetes mellitus (yes/no)	2.37	1.61-3.51	♭0.001
	Non-cardiac origin		
	HR	CI (95%)	p
Male sex	1.86	1.25-2.78	0.002
Age (years)	1.09	1.06-1.13	♭0.001
Smoking (yes/no)	2.05	1.33-3.15	0.001
Antihypertensive treatment (yes/no)	2.25	1.46-3.46	♭0.001
Obesity (yes/no)	2.37	1.51-3.71	♭0.001

CAD = coronary artery disease, HR = hazard ratio.

mechanisms are possible; many patients in Sweden with atrial fibrillation are treated with anticoagulants [18]. This would protect against pulmonary embolism [19] and may therefore increase survival. Another possibility is that patients with arrhythmia are more prone to be admitted to a ward with telemetry, which is also known to increase survival [20].

One of the limitations of this study was that the participants of the MDCS were healthier than the non-participants, the incidence of cancer and the total mortality were lower among the participants [21]. Age was not significantly associated with survival in this study, but a clear limitation concerning this variable was a selection bias since only patients between 44 and 74 years of age were included in the MDCS-material. Another possible source of selection bias was that cases of CA potentially were missed between the inclusion to the MDCS (1991–1996) and the start of the local CA registry (1999). Unfortunately, post-arrest variables such as hypothermia and invasive coronary angiography, which could affect the survival data were not recorded in this study.

Competing risk is another possible limitation that possibly could weaken the associations between risk factors and CA. However, we find it unlikely that the observed associations are exaggerated.

Furthermore, our previous finding that heart rate and sodium were significantly associated with survival [20] could not be validated, due to missing data for these variables.

In conclusion, apart from smoking, which increases the risk of cardiac arrest in general, the midlife risk factor pattern differs between arrest of cardiac and non-cardiac origin. Whereas cardiac arrest of cardiac origin is predicted by history of cardiovascular disease, dyslipidemia and diabetes mellitus, the main risk factors for cardiac arrest of non-cardiac origin are obesity and hypertension. In addition to control of classical cardiovascular risk factors for prevention of arrest of cardiac origin, our results suggest that prevention of midlife obesity may reduce the risk of cardiac arrest of non-cardiac origin.

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Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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Table 4
Univariate analysis of survival, factors at arrest.

Variable	Survival (n = 65), n (%)	Non-survival (n = 313), n (%)	p
Age (years)‡	73.7 (7.7)	75.3 (9.6)	0.505†
Male sex	42 (64.6)	207 (66.1)	0.814*
Telemetry (yes/no)	19 (29.2)	53 (16.9)	0.022*
Shockable rhythm (yes/no)	49 (75.4)	50 (16.0)	♭0.001*
STEMI (yes/no)	21 (32.3)	55 (17.6)	0.007*
OHCA (yes/no)	26 (40.0)	214 (68.4)	♭0.001*
Cardiac origin (yes/no)	57 (87.7)	215 (68.7)	0.002*
History of stroke (yes/no)	9 (13.8)	40 (12.8)	0.816*
History of CAD (yes/no)	43 (66.2)	169 (54.0)	0.072*
History of heart failure (yes/no)	19 (29.2)	46 (14.7)	0.005*
History of atrial fibrillation or flutter (yes/no)	24 (36.9)	62 (19.8)	0.003*
History of diabetes mellitus (yes/no)	16 (24.6)	77 (24.8)	0.970*

* = Chi square, † = Mann-Whitney, ‡ = median (interquartile range).
CAD = coronary artery disease, OHCA = out-of-hospital cardiac arrest, STEMI = ST-elevation myocardial infarction.

Table 5
Multivariate model of survival, factors at arrest.

Variable	OR	CI (95%)	p
Shockable rhythm (yes/no)	16.04	7.92–32.47	♭0.001
Cardiac origin (yes/no)	2.80	1.05–7.48	0.041
OHCA (yes/no)	0.20	0.10–0.41	♭0.001
History of atrial fibrillation or flutter (yes/no)	2.32	1.15–4.65	0.019

Adjusted for sex and age.
OHCA = out-of-hospital cardiac arrest, OR = odds ratio.

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Paper IV